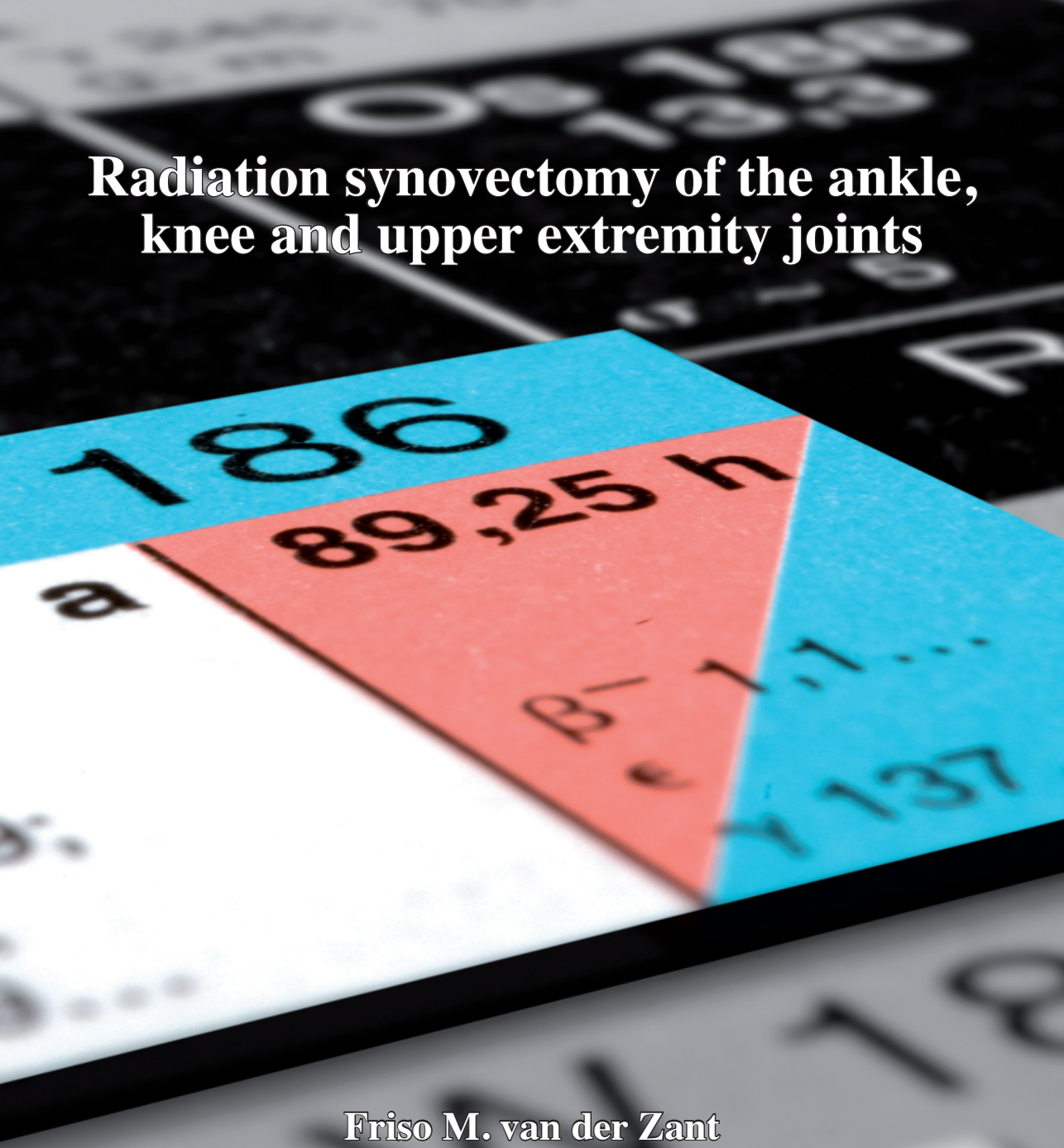
Radiation synovectomy of the ankle, knee and upper extremity joints



Friso M. van der Zant

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Radiation synovectomy of the ankle, knee and upper extremity joints

Radiatiesynovectomie van enkel, knie en gewrichten van de bovenste extremiteit

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. J.C. Stoof in gevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 4 december 2008 des middags te 12.45 uur

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Friso Martijn van der Zant
geboren op 6 december 1964
te Amersfoort

Promotor: Prof. dr. J.W.J. Bijlsma
Co-promotor: Dr. J.W.G. Jacobs

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To Lukie van der Zant-Paulides
Menno Strijers
Solange
Maurits

Contents

Chapter 1

Introduction and outline of this thesis

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Prevalence of arthritides and treatment strategies

The most common type of inflammatory arthritis is rheumatoid arthritis (RA), affecting about 1% of the population worldwide. Prevalence rates range from 0.3% of the population in China to 5% in the Pima Indian population in the USA (1). Although there are a variety of extra-articular manifestations of RA, it is considered to be primarily a joint disease. The hallmark of RA is synovitis, an inflammation of the synovial membrane covering the joint. Inflammatory arthritic diseases other than RA can also cause synovitis, including psoriatic arthritis and oligo-arthritis of unknown origin. In people over the age of 15, psoriatic arthritis has an annual incidence of 6 cases per 100,000 (2,3); the prevalence is 1 case/1000 persons (3). Osteoarthritis is a very common degenerative joint disease that predominantly affects the elderly. Knee osteoarthritis is the most common, with an incidence rate of approximately 240 cases per 100,000 person-years (4).

Arthritis is a common and often chronic condition that can be managed with both local and systemic drug treatment. The latter includes nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) including biological agents and glucocorticoids (GCs). A well known local therapy is intra-articular GC injection. In addition to drug treatment, physiotherapy, braces and life style changes may be recommended as well. If chronic synovitis persists after these non-invasive strategies, surgical, chemical, or radiation synovectomy may be an option. Common indications for synovectomy are chronic inflammatory arthritides (eg, RA, psoriatic arthritis), non inflammatory disorders (eg, osteoarthritis, osteochondromatosis, pigmented villonodular synovitis) and recurrent hemartrosis (eg hemophilia).

Surgical synovectomy to remove inflamed joint tissue has evolved from open to arthroscopic techniques the past years, and is successful in 40-90% of treated patients. The duration of local remission or clear regression of arthritis varies from several months up to more than 10 years (5-11). Chemical synovectomy, which involves the injection of chemicals into the joint, was first described in 1951; the authors used osmic acid (12). This is a strong oxidizing agent, which deposited in inflamed synovial tissue and synovial fat induce necrosis of the inflamed synovial membrane. The results of chemical synovectomy are variable, but satisfactory disease control can be achieved (13-16). Finally, for radiation synovectomy which is the focus of the investigations described in this thesis, radionuclides are injected into the inflamed joint to treat synovitis. This technique is discussed in greater detail in the following section.

Radiation synovectomy

The first publication about the administration and action of intraarticularly injected radionuclides on the synovial membrane dates back to 1924 (17), and the first clinical results of radiation synovectomy (also called radiosynoviorthesis; RSO) were published by

Fellinger et al. in 1952 (18). The small particles labelled with β-emitting isotopes injected intra-articularly at RSO are subsequently engulfed by macrophage-like synoviocytes and phagocytizing inflammatory cells located in the subsynovial connective tissue (19). Radiation of the synovium results in synoviocyte and inflammatory cell necrosis and inhibited cell proliferation. Synovitis and possibly also progression of joint damage can be halted temporarily by RSO (20). Several radioisotopes have been proposed for RSO; the European Association of Nuclear Medicine (EANM) recommends ^{90}Yttrium, ^{169}Erbium, and ^{186}Rhenium colloids (21). These radiopharmaceuticals are currently the only commercially available isotopes for RSO in Europe.

The penetration depth of the radiation emitted by the radionuclide should correspond to the thickness of the inflamed synovium in the treated joint in order for RSO to be effective. In soft tissues, the mean and maximum penetration depths of β-rays from ^{90}Yttrium ($t_{1/2}$: 2.7 days) are 3.6 and 11 mm, respectively. The corresponding penetration depths of the β-rays from ^{186}Rhenium ($t_{1/2}$: 3.7 days) are 1.2 and 3.7 mm, and for ^{169}Erbium ($t_{1/2}$: 9.4 days), the mean and maximum penetration depths are 0.3 and 1.0 mm. Because of these properties, ^{90}Yttrium is used for RSO of the knee, ^{186}Rhenium for medium-sized joints (such as the gleno-humeral joint, elbow, radio-carpal joint, hip, and tibio-tarsal joint), and ^{169}Erbium for finger and toe joints. In addition to β-rays, ^{186}Rhenium also emits γ-photons (energy, 137 KeV), which do not contribute to the therapeutic effect. The physical characteristics of the radionuclides used for RSO are summarized in Table 1.

Table 1. Physical characteristics of the radionuclides used for RSO as recommended by the European Association of Nuclear Medicine.

Nuclides	T1/2 (hours)	Energy (MeV)		Penetration of β radiation in synovium (mm)		in cartilage (mm)
		γ	β	Mean	Max	Max
Yttrium-90	65	-	2.27	3.6	11.0	2.8
Rhenium-186	89	0.137	1.07	1.2	3.7	0.9
Erbium- 169	226	-	0.34	0.3	1.0	0.2

One drawback of RSO is leakage of the radionuclides to non-target organs. Theoretically, the grade of hypervascularity and/or hyperpermeability could influence leakage, especially if the radiocolloids are chelated. The smaller radionuclides can enter the bloodstream more easily. By adding GC to the radiocolloids for RSO, hypervascularity as a consequence of

inflammation can be diminished and leakage inhibited. In addition to possibly inhibiting leakage by quickly diminishing hypervascularity by reducing the inflammation, the anti-inflammatory effects of GC can bridge the lag phase from the moment of injection to the point in time the β-irradiation starts to have an effect. GC also lowers the risk of radiation-induced synovitis. The nuclide dose for each joint as recommended by EANM and the triamcinolone acetonide dose used at our institution are shown in Table 2.

Table 2. The nuclide dose for each joint as recommended by the European Association of Nuclear Medicine and the triamcinolone acetonide (TA) dose used at the Medical Center Alkmaar.

Joint	Administered MBq			Recommended volume (ml)	Co-administered TA (mg)
	Yttrium-90	Rhenium-186	Erbium- 169		
Knee	185-222			3-5	40
Shoulder (gleno-humeral)		74-185		3	40
Elbow		74-111		1-2	40
Wrist		37-74		1-1.5	12
Ankle (tibo-talar)		74		1-1.5	40
Subtalar		37-74		1-1.5	40
Metacarpo-phalangeal			20-40	1	8
Meta-tarsophalangeal			30-40	1	8
Proximal interphalangeal			10-20	0.5	4

The advantages and disadvantages of exposure to radiation should be weighed carefully when using RSO. Whole body radiation exposure can be monitored using the incidence of chromosomal aberrations as a biological marker. One study found 25 dicentric chromosomes in 10,000 cells (0.25%) before RSO with ^{90}Yttrium and afterwards 41 (0.41%) (22). This

difference was not statistically significant. A seven-year study by Vuorela et al. compared the risk of developing a malignancy in 143 patients treated with ^{90}Yttrium-RSO versus 1085 patients who did not undergo ^{90}Yttrium-RSO treatment (23). The standardised incidence ratio of cancer was 0.6 with a 95% confidence interval (CI) 0.3 to 1.1 for patients who received ^{90}Yttrium, versus 1.1 (95% CI 0.9 to 1.3) for the patients who did not, Thus ^{90}Yttrium treatment for RSO did not statistically significantly increase the risk of cancer.

Other adverse effects of RSO are local mild transient local pain and/or swelling. These adverse effects were described in one study as occurring in up to 24% of patients treated with RSO (24). However, other studies have found a lower incidence, with some reporting no local adverse reactions at all (25-29). A needle tract burn, which is a radiation burn of the needle tract caused by back-flushing of the radioisotope is a rare adverse effect of RSO, sometimes resulting in a fistula (30); thrombosis and joint infection are two other rare but serious adverse effects (30).

Response rates one year after RSO of 40-80% have been reported with a decline in symptom control over time (31). A meta-analysis of 26 studies and a total of 2190 treated joints indicated that RSO was effective in 70% (32). The latter two publications included also RSO with unusual radiocolloids like ^{32}Phosphorus, ^{165}Dysprosium and ^{198}Gold colloids. Two literature reviews, in 1993 and 2000, did not favour the use of ^{90}Yttrium colloid RSO of the knee compared to treatment with GC, osmic acid, or surgical synovectomy (33,34). Two other reviews supported the effectiveness of RSO of the knee with ^{90}Yttrium and RSO of medium-sized joints with ^{186}Rhenium (35,36).

The above mentioned results are often of RSO without co-administration of GC and/or without failure to previous intra-articular GC injection. Therefore, these results are not mirroring current clinical practice, in which RSO is performed in patients in whom the disease as a whole is fairly well controlled with only one or at most a few joints resistant to systemic therapy and one intraarticular GC injection given as outpatient. Furthermore, the results of RSO are predominantly based on the results of RSO of knee and finger joints, while RSO is an option in other joints too, in which RSO could show different efficacy. Other sources of differences in results of studies are leakage of the radionuclide from the joint and the distribution of the radionuclide within the joint. Up till now these aspects of RSO have not been studied.

In this thesis the results of RSO not only of the knee, but also of the ankle and the upper extremity joints with ^{90}Yttrium, ^{169}Erbium, and ^{186}Rhenium colloids as advised by the EANM are studied. Leakage and distribution of the radionuclide are analyzed and a systematic literature review is performed to evaluate the evidence for RSO.

Thesis outline

First, this thesis describes a retrospective study of the effect, effect duration, and safety of RSO of the ankle (tibio-talar joint) with 75 MBq colloidal ^{186}Rhenium sulfide. Nuclide leakage from the joint is analyzed and extra-articular radiation is discussed.

Second, in a randomised, double-blind, placebo-controlled study the efficacy of treating joints of the upper extremity with intra-articular radionuclide plus GC with that of intraarticular placebo plus GC are compared. Differences in outcome in patients with RA versus non-RA patients and between patients with more and those with less radiological joint damage are analyzed. Adverse effects are evaluated and prediction of clinical effects is analyzed.

Third, this thesis describes in a prospective study on the influence on the clinical effect of RSO in joints of the upper extremity of leakage of nuclides to non-target organs. This study also looks at differences in leakage between ^{186}Rhenium and ^{169}Erbium and prediction and dosimetry of leakage.

Fourth, the impact of intra-articular distribution of ^{90}Yttrium in the knee joint on the clinical effect of RSO and on leakage from the joint is described. This study was part of a Dutch multi-centre, double-blind, placebo-controlled, randomized clinical trial comparing the clinical effect of intraarticular ^{90}Yttrium and GC versus that of placebo and GC.

Lastly, this thesis discusses the current recommendations for RSO and analyzes the evidence for RSO efficacy for different joints and nuclides in a systematic review of the literature.

In summary, is RSO of the knee, the ankle and upper extremity joints effective and is it evidence based? Which factors determine the effect of RSO? Are leakage and inhomogeneous distribution of the radionuclide clinically important?

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Chapter 2

Radiation synovectomy of the ankle with 75 MBq colloidal ^{186}Rhenium-sulfide: effect, leakage, and radiation considerations

J Rheumatol. 2004;31:896-901

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Abstract

Objective.

In a retrospective study we evaluated the effect, duration of effect, and safety of radiosynoviorthesis of the ankle in patients with persistent synovitis, refractory to disease modifying antirheumatic drugs (DMARD) and intraarticular glucocorticoid injections. We estimated leakage and dose to target and non-target organs.

Methods.

Radiation synovectomy was performed by injection of 75 MBq ^{186}Rhenium colloid and 20 mg triamcinolone-hexacetonide mixed in a volume of about 1.5 ml. About 24 hours after injection, leakage of the radionuclide was measured with a single-head gamma camera, with views of the ankle joint, regional (inguinal) lymph nodes, and liver. Leakage was expressed as counts in the target region of interest corrected for background relative to total counts corresponding with percentage of injected dose. The effect of radiosynoviorthesis was scored into 3 categories: (1) No effect, i.e., persistent synovitis or only minimal reduction of swelling and/or pain, or the need of intraarticular glucocorticoid injection within 3 months or arthrodesis of the treated joint within 6 months. (2)

Moderate effect, i.e., significant reduction of swelling, pain, and improvement of function. (3) Good effect, i.e., complete or almost complete remission of synovitis.

Results.

The mean age of patients (28 women, 12 men) at the time of treatment was 58 years (range 33–76); 54 consecutive procedures in ankles of the 40 patients were evaluated. No effect was found in 12 of 54 (22%) treated joints; moderate effect in 12 (22%), with a mean duration of effect of 34 months (range 12–49); and good effect in 30 (56%), with a mean duration of effect of 41 months (range 21–75). Mean effect-duration did not differ significantly between the moderate and good effect groups. Mean leakage did not differ significantly between the effect groups.

Conclusion.

Radiation synovectomy of the ankle is a safe and effective treatment in persistent synovitis, although all patients eventually experienced recurrence of arthritis.

Introduction

Chronic rheumatic inflamed joints resistant to therapy with nonsteroidal antiinflammatory drugs (NSAID), disease modifying antirheumatic drugs (DMARD), and intraarticular glucocorticoid injections may be controlled with synovectomy. Three types of synovectomy are known: chemical, surgical, and radiation.

Osmic acid is the most frequently used agent for chemical synovectomy. The results are variable, but satisfactory disease control can be achieved[1-3]. Osmic acid etches the synovial intimal lining cells, inducing atrophy of the synoviocytes and reduction of inflammation[4,5].

Surgical synovectomy is successful in 40–90% of treated patients, although the duration of remission varies from a relatively short period up to many years[6-10]. Surgical synovectomy has evolved from open to arthroscopic techniques. A new technique is arthroscopic laser synovectomy that reduces bleeding of the synovium. However, not all joints are accessible for arthroscopic synovectomy. Surgical synovectomy in addition has the drawback that a long revalidation period is necessary after surgery.

Radiation synovectomy or radiosynoviorthesis has been used for decades. Intraarticularly injected small particles labelled with ß-emitting isotopes are phagocytized by macrophage-like synoviocytes and by phagocytizing inflammatory cells in the subsynovial connective tissue[11].

Radiation of the synovium results in necrosis of the synoviocytes and inflammatory cells, and cell proliferation is inhibited. Temporarily, the cycle of synovitis and joint damage can be halted[12]. Satisfactory control of synovitis is achieved in 40–80% of patients after one year, with a decline over time[13-18].

Estimation of the effect of radiation synovectomy or radiosynoviorthesis is mainly based on studies of knee joints. Studies on other joints are rare; the ankle (tibiotalar) joint has been investigated in only a few studies. To our knowledge, only 4 articles in the English literature include results of radiosynoviorthesis of the ankle[16,19-21], besides some studies of hemophilic ankle arthropathy[22,23]. In our retrospective study we evaluate the size and duration of the effect and safety of radiation synovectomy of the ankle. For this latter purpose, leakage to non-target organs and dose to target and non-target organs was measured.

Materials and methods

Patients.

In the Medical Centre Alkmaar, a 913-bed non-university teaching hospital, patients with persistent synovitis refractory to DMARD and at least one intraarticular glucocorticoid injection (20 mg triamcinolone- hexacetonide) are referred to the nuclear medicine department for radiation synovectomy. In the period 1990 to 1996 all 54 consecutive procedures in ankles of 40 patients could be evaluated. The characteristics are summarized in Table 1. The mean age of the patients at the time of treatment was 58 years (range 33–76 yrs). The female:male ratio

of the 40 patients was 28:12. In 10 patients both ankles were treated, and in 3 patients (in one, both ankles) a second radiosynoviorthesis in the same joint was performed. The underlying disease causing synovitis was rheumatoid arthritis (RA) in 49 cases, psoriatic arthritis in 3, posttraumatic arthritis in one, and reactive (Yersinia) arthritis in one. From the patient's chart the following data were obtained: age, sex, rheumatic disease causing the synovitis, global opinion from the treating physician, and if available, inflammatory joint measures (pain, swelling/hydrops, and range of motion) and side effects (needle tract burn, radiation induced flare of synovitis).

The effect of radiosynoviorthesis was scored into 3 categories: (1) No effect, i.e., persistent synovitis or only minimal reduction of swelling and/or pain, or the need of an intraarticular glucocorticoid injection within 3 months or arthrodesis of the treated joint within 6 months (Group 1). (2) Moderate effect, i.e., significant reduction of swelling and pain, and improvement of function (Group 2). (3) Good effect, i.e., complete or almost complete remission of synovitis (Group 3). The patients' radiographs were reread by the first author and scored according to the radiological Steinbrocker classification[24]. The duration of the effect was defined as the interval until clinical recurrence of synovitis, considerable worsening of the joint inflammatory indicators, or the need for an intraarticular glucocorticoid injection.

Table 1: Characteristics of 54 synovectomies in 40 patients.

Mean age in years (SD, range)	58 (11, 33-76)
Gender F/M (% female)	36/18 (67)
Right/left ankle (% right)	35/19 (65)
	Diagnosis: Number (%), ankles
Rheumatoid arthritis	49 (91)
Psoriatic arthritis	3 (6)
Posttraumatic arthritis	1 (2)
Reactive (Yersinia) arthritis	1 (2)

Radiosynoviorthesis procedure.

Radiation synovectomy was performed under sterile conditions. After puncture of the tibiotalar joint (ankle), synovial fluid was aspirated if present. Aspiration was performed to avoid back-flushing due to high hydrostatic pressure and to confirm correct intraarticular needle positioning. If needed, local anesthesia with 2% lidocaine was given. Arthrography with small amounts of x-ray contrast medium was performed to confirm intraarticular needle position just before injection of 75 MBq ^{186}Rhenium colloid (RE-186-MM-1; CIS Bio International, Gif sur Yvette, France) and 20 mg triamcinolone-hexacetonide mixed in a volume of about 1.5 ml. In our institution, glucocorticoids are coadministered to avoid radiation induced flare of synovitis and to bridge the lag phase of the onset of effect of radiosynoviorthesis. Further, glucocorticoids can reduce inflammation of the synovium and thus vascularization, diminishing leakage of the radiopharmaceutical to non-target organs. The syringe was flushed with 0.9% NaCl before withdrawal, to minimize the chance of "needle tract burn" (a ß-radiation induced skin lesion or fistula caused by backflushing of the radioisotope through the needle tract). The ankle was immobilized by a bandage for 72 hours.

Leakage measurements.

Roughly 24 hours after the injection, leakage of the radionuclide was measured with a single-head gamma camera. Views of the ankle joint, regional (inguinal) lymph nodes, and liver were obtained with the following acquisition variables: time 150 s, peak 1: 140 keV with a window of 15%; peak 2: 62 keV with a window of 20% (for measuring Brehmmstrahlung), matrix 256 × 256. Regions of interest (ROI) were drawn around target areas and background areas. Leakage was expressed as counts in the target ROI corrected for background relative to total counts corresponding with percentage of injected dose.

Dosimetry. For radiation synovectomy, the dose D_{syn} in the synovium can be determined using the equation:

$$D_{syn} = \frac{A_{syn} F}{\lambda_n S_{syn}} \qquad (1)$$

where A_{syn} = total activity in the synovium, λ_n = nuclear decay constant of the radionuclide, and F = absorbed dose constant (in Gy cm^2 MBq^{-1} s^{-1})[25].

For ankle joints S_{syn} = 44 cm2 (surface of the synovium of the ankle)[26].

Given the distribution of the radionuclide in the body, it is possible to calculate the dose to the whole body as well as to different organs. As ^{186}Re emits γ- and ß-radiation, each should be considered separately.

The tissue penetration of ß-radiation (electrons) is within the range of millimetres. Assuming that organs are larger than the average range r_{avg}^{β} of electrons, the dose $D_{org}^{ß}$ is given by:

$$D_{org}^{\beta} = 1.6 * 10^{-10} \frac{A_{org}}{\lambda_n} \frac{\sum y_i E_i}{m_{org}} \quad (2)$$

in which A_{org} = total activity in the organ, y_i = fraction of energy E_i in the decay spectrum, λ_n = the nuclear decay constant, and m_{org} = the mass of the organ. In situations where the biological decay constant λ_{biol} is small compared to the nuclear decay constant λ_n, the effective decay constant $\lambda_{eff} = \lambda_n + \lambda_{biol}$ should be used instead:

$$D_{org}^{\beta} = 1.6 * 10^{-10} \frac{A_{org}}{\lambda_{eff}} \frac{\sum y_i E_i}{m_{org}} \quad (3)$$

As r_{avg}^{β} for ^{186}Re is around 1.2 mm, the assumption holds for all organs, except for lymph nodes.

As the diameter of a lymph node is within the (average) range of an emitted electron, a correction is necessary. Assuming that continuous slowing down approximation holds, the fraction of the dose deposited in a small organ follows from:

$$D_{lymph}^{\beta} = D_{org}^{\beta} \frac{r_{lymph}}{r_{avg}^{\beta}} \quad (4)$$

with r_{lymph} the (average) radius of the lymph node.

Compared to ß-radiation, γ-radiation (photons) has much greater tissue penetration. Indeed, the whole body can be seen as the target and consequently, dose will be deposited over the whole body. Given the localization of the radionuclide (in the ankle) and the energy of this γ-radiation (137 keV), the resulting dose in the lower trunk (first localization to find organs at risk) can be estimated. Very important for this dose is the transmission through the leg, which can be calculated as:

$$I_d = I_o e^{-\mu d} \quad (5)$$

where I_o = initial intensity, I_d = intensity after d cm of tissue with an absorption coefficient μ. For a leg with a length of 70 cm, the transmitted portion of radiation is < 0.01%. Therefore, the contribution of γ-radiation from the ankle to the trunk can be ignored. For the smaller portion of leaked radionuclide (e.g., = 5% to the liver), the contribution to the dose of the organs at risk can also be neglected. This means, that for this particular situation (radiation synovectomy of the ankle), the contribution of γ-adiation to the dose of the organs at risk can be ignored.

The equivalent body dose E_{body} can be calculated with the tissue weight factor w_T as defined by the International Commission on Radiological Protection (ICRP) and the tissue dose D_T using[27]:

$$E_{body} = \sum w_T D_T \quad (6)$$

According to this ICRP model, liver and ankle do have a contribution to the equivalent body dose, but solitary lymph nodes have no contribution.

With the equivalent body dose E_{body} it is possible to estimate the total risk of the treatment.

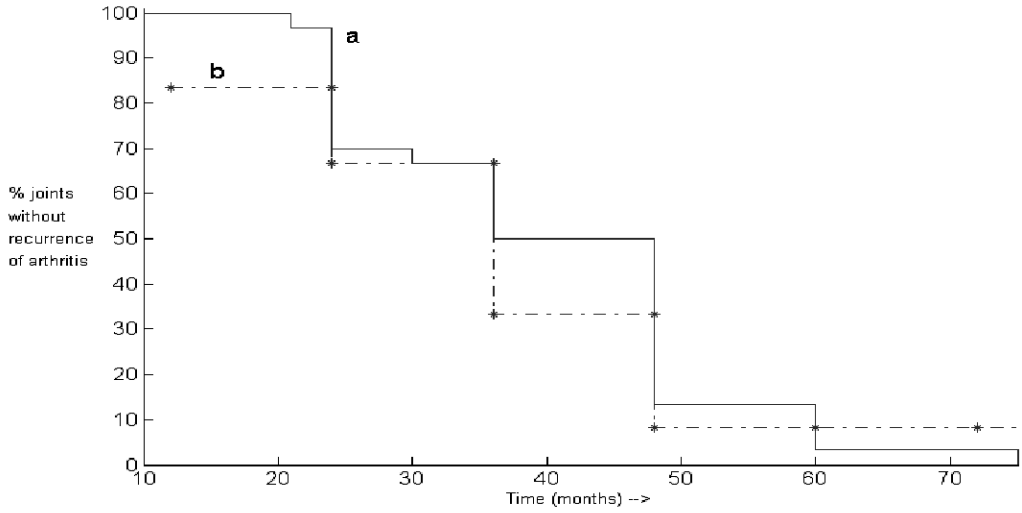
Statistics. The one-sample Kolmogorov-Smirnov test was used to test continuous data for normal distribution and the Kolmogorov-Smirnov Z test was used to test the distribution of groups. Continuous data (leakage and response time) of groups were tested for statistically significant difference with analysis of variance (ANOVA) or 2-sample T tests in case of normal distribution of the data and otherwise with Mann-Whitney U tests. Ordinal data like Steinbrocker radiological classifications were tested for statistical significance with Fisher's exact test. Statistical significance was defined as $p < 0.05$.

Results

Radiation synovectomy resulted in no effect or only minimal reduction of swelling and/or pain in 12 (22%) of the treated joints (Group 1); a moderate effect, i.e., significant reduction of swelling and pain and improvement of function in 12 (22%; Group 2); and a good effect, i.e., complete or almost complete remission of synovitis in 30 (56%; Group 3). The mean duration of effect for Group 2 was 34 months (range 12–49 mo) versus 40 months (range 21–75 mo) for Group 3. Although the duration of effect seems to be in favor of Group 3, it did not differ significantly between Groups 2 and 3. Survival curves for the moderate and good effect categories are illustrated in Figure 1. Radiation synovectomy was repeated in 3 patients 11,

14, and 36 months after the first treatment. In one patient neither synovectomy had any effect. In the other 2 patients both procedures showed a good effect; in these patients the duration of effect was longer for the second synovectomy. The duration of the first treatment in these 2 patients was 11 and 16 months and of the second treatment 25 and 36 months.

Figure 1: Survival curves for the effect categories moderate and good effect; percentage of joints with persistent effect in time.



Curve a: good effect group. Curve b: moderate effect group. The duration of effect did not significantly differ between the good and moderate effect categories.

In this study no short-term side effects were recorded. Side effects in the longer term caused by leakage have not been reported, although the followup period for late effects is too short. The immobilization and hospitalization for 3 days were experienced as only slightly inconvenient by the patients. No thromboembolic events have been reported in the first 3 months after synovectomy.

At the time of treatment the Steinbrocker radiological classification was 1 or 2 in 43 (80%) joints and 3 or 4 in 11 (20%) joints. Radiation synovectomy failed in 5 (12%) of 43 treatments in joints with radiological classification 1 or 2, and in 7 (64%) of 11 treatments in joints with radiological classification 3 or 4 ($p = 0.001$), as described in Table 2.

Table 2: Effect of synovectomy versus radiological classification.

		Steinbrocker Radiological Classification		
		1 or 2	3 or 4	Total
Effect of synovectomy	No or minimal	5	7	12
	Moderate or good	38	4	42
	Total	43	11	54

Fisher exact test P=0.001

Data on leakage (as percentage of injected dose) to lymph nodes and liver are shown in Table 3. As expected, leakage to lymph nodes occurred more often than leakage to the liver; mean leakage was higher in lymph nodes than in liver. Of all procedures, maximal leakage to a single lymph node was 4% and to the liver 5.5%. "Total leakage" was defined as the sum of leakage to lymph nodes and liver.

Mean "total leakage" and variance did not differ significantly in the 3 effect groups (by ANOVA), nor was there a significant difference between radiological classification 1 or 2 and 3 or 4 (independent 2-sample T tests).

The dose to the synovium of the ankle was 3.05 Gy and lowered to 2.76 Gy in case of leakage of 9.5%. Leakage of maximal 4% to a single lymph node gives a dose of 35 Gy and maximal dose to the liver was 0.0075 Gy. Given that the tissue weight factor (a concept devised by the ICRP to translate a partial radiation dose into a whole-body dose) for both ankle and liver is 0.05, the equivalent body dose E_{body} will be 0.15 mSv (no leakage) or 0.14 mSv (9.5% leakage), which means no substantial difference. Compared to a dose of 5.0 mSv received from a chest computer tomography (CT) scan, this is a low dose. It is somewhat higher than a dose of 0.01 mSv received from a radiograph of the ankle[28].

Table 3: Leakage (as percentage of injected dose) to lymph nodes, liver and total leakage (defined as summation of leakage to lymph nodes and liver) in the different effect-groups.

	No effect Group 1	Moderate effect Group 2	Good effect Group 3	For all 54 treatments
Leakage to Lymph nodes				
Mean (SD)	2.6 (3.1)	2.1 (3.2)	2.4 (2.9)	2.4 (3.0)
Range	0-9.6	0-8.8	0-9.5	0-9.6
Leakage to liver				
Mean (SD)	1.6 (2.3)	0.5 (0.2)	0.9 (1.7)	0.8 (1.7)
Range	0-5.5	0-0.7	0-5.5	0-5.5
Total leakage				
Mean (SD)	4.2 (2.9)	2.1 (3.2)	3.3 (3.2)	3.2 (3.2)
Range	0-9.6	0-8.8	0-9.5	0-9.6

Discussion

Inflammatory joint diseases, most commonly RA, generate high costs. The clinical effect of radiation synovectomy, using different isotopes, has been studied for decades.

Deutsch, et al summarized the results of 64 studies. In these mainly retrospective studies, good effect after one year is achieved in 40–90% of subjects[15]. To our knowledge, in the English literature only 4 studies have described results of radiation synovectomy of the ankle[16,19-21]. In some studies results of different joint are presented, but the effect of radiation synovectomy of the ankle has not been described separately[29- 31]. In the 4 studies above, radiosynoviorthesis was effective in 90% (9 out of 10)[19], 17% (4/23)[16], 53% (8/15)[20], and 62% (19/26)[21] of subjects. In 2 studies colloidal ^{186}Rhenium-sulfide was used[20,21], in one ^{32}P-colloidal chromic phosphate[19], and in one ^{90}Yttrium colloid[16]. In our study moderate or good effect was achieved in 78% (42 out of 54) of the procedures. There is a difference in effect rate between our study (78%) and the 2 studies using colloidal ^{186}Rhenium-sulfide, with an effect rate of 53% and 62%, Respectively[20,21]. The explanation of this difference could be that one study did miss patient data in 42% (11 out of 26) of treatments[20], and in the other study 31%

(8 of 26) did not have RA compared to 9% (5 of 54) in our study[21]. In patients with RA, 78% (14 of 18) of the treated joints did show moderate or good effect[21].

In other reports the duration of the effect of radiosynoviorthesis is scarcely described and data for the ankle are not available. In one study the mean duration of remission in knee joints was 21 months (range 1–95 mo)[17]. In our study the mean duration of effect in ankle joints was 34 months in the group with moderate effect and 40 months in the group with good effect.

Surgical, especially arthroscopic, synovectomy followed by radiation synovectomy 4 to 6 weeks postoperatively should theoretically give a more radical reduction of inflammatory activity, resulting in a higher success rate and a longer disease-free period, although to our knowledge no studies have been performed to confirm this. Leakage from the treated joint is one drawback of radiation synovectomy and can lead to radiation especially of lymph nodes. No late clinical effects of radiation synovectomy have been described in previous reports, although they have not been studied systematically, probably because such a study would extend over many decades. However, early effects, i.e., chromosomal aberrations, after radiosynoviorthesis have been described[32,33]. In our experience little leakage is seen after radiosynoviorthesis of finger joints with ^{169}Erbium or knees with ^{90}Yttrium. In contrast, leakage is more often seen in radiosynoviorthesis of other joints with ^{186}Rhenium, despite arthrographic control, and using the least traumatic injection technique and immobilization for 72 hours.

Particle size is an important factor in leakage: bigger particles show fewer tendencies to leakage. The appropriate size is considered to be 2 to 5 μm[34]. In Europe, 3 products are commercially available. The size of colloidal ^{186}Rhenium-sulfide is 50–300 nm, ^{90}Yttrium colloid 200 nm, and ^{169}Erbium 2000–3000 nm (CIS Bio International), or 100 nm for ^{90}Yttrium colloid (Amersham Healthcare, Little Chalfont, Buckinghamshire, UK). Radioactive gold particles of 20 nm size did show leakage to lymph nodes in 30%, whereas particles of 300 nm did not show leakage to lymph nodes[35-38]. In some reports a maximal leakage of 48% to lymph nodes has been described, although the smallest particles were not designed for radiation synovectomy[35]. In some studies other agents (not commercially available) with larger particle sizes than above have been used. Maximal leakage varied from 3% for ^{153}Samarium hydroxyapatite, with particle sizes 16–22 μm, to 9% for ^{165}Dysprosium hydroxide macroaggregate, with particle sizes 2–5 μm[39,40].

In another study with ^{166}Holmiun polymeric microspheres (particle sizes 2–13 μm), minimal retention in the joint was 95% of the injected dose, i.e., leakage to non-target organs was less than 5%[41].

Dosimetry, using theoretical models, gives a fairly good impression of the radiation dose and risk. Using the equivalent body dose (E_{body}), it is possible to determine the risk of death or the loss of years because of the use of radiation. The risk of dying from radiation is currently set to 10^{-2}/Sv, which means the risk of dying is 1% when receiving an equivalent body dose

of 1 Sv. For radiosynoviorthesis of the ankle the equivalent body dose is around 0.15 mSv, leading to risk of 1.5 x 10^{-6} of death through radiation. As the averaged loss of years is 13 years for each case of death, an equivalent body dose of 0.15 mSv results in 0.002 years (= 0.7 day) loss of life, which can be ignored. The same conclusion can be drawn comparing the risk of radiosynoviorthesis of the ankle with the normal risks of life and of a CT examination of the chest and a radiograph of the ankle (Table 4).

Table 4: Risk of radiosynoviorthesis compared to other activities.

	Risk (death per 10000 per year)
Smoking 10 cigarettes per day	18
Traffic	2.3
Homework	1.6
CT-chest examination	0.5
Radiosynoviorthesis of the ankle joint	0.02
X-ray of the ankle	0.0001

Retrospective studies have several limitations, in particular, how are criteria on which improvement is made derived? It is preferable to assess outcome measurements on validated criteria such as proposed by the American College of Rheumatology. Such outcome assessment is not necessarily available in retrospective studies and is a major limitation.

Clinical judgment of the treating physician is subject to bias. Therefore in our study complementary to this we used the more objective criteria “need of an intraarticular glucocorticoid injection within 3 months” and “arthrodesis within 6 months” for no effect, and “time to next intraarticular corticosteroid injection” as duration of effect.

Despite the limitations of our study we suggest radiation synovectomy of the ankle is safe and effective but temporary treatment in persistent synovitis refractory to DMARD and intraarticular glucocorticoid injection.

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Chapter 3

Clinical effect of radiation synovectomy of the upper extremity joints: a randomised, double-blind, placebo-controlled study

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Abstract

Purpose.

To compare the clinical efficacy of radiosynoviorthesis (RSO) with intra-articular radionuclide plus glucocorticoid (GC) injection (group A) with that of placebo plus GC injection (group B) for the treatment of persistent synovitis in joints of the upper extremity.

Methods.

At baseline and at 6 and 12 months after intraarticular injection, six clinical parameters were scored.

Changes in clinical values over time were summed to provide a change composite index (CCI), ranging from 0 (no effect) to 12 (maximal effect). A CCI ≥6 was considered to indicate successful treatment. Differences in response rate and CCI between groups A and B were examined. Regression analyses were performed to explore whether baseline variables could predict therapeutic effect.

Results.

Sixty-eight joints in 44 patients were treated. Six months after intra-articular injection, response rates (CCI ≥6) were 69% (25/36) in group A and 29% (9/31) in group B (p=0.001). The mean CCIs ± standard deviation at 6 months were 6.7±3.2 for group A and 3.3±3.8 for group B (p=0.001). At 12 months the response rates were 69% (25/36) in group A and 32% (8/25) in group B (p=0.004). The mean CCIs at 12 months were 6.8±3.3 for group A and 4.2±4.7 for group B (p= 0.046). None of the baseline variables predicted the therapeutic effect.

Conclusion.

RSO (radionuclide plus GC) of upper extremity joints with immobilisation for 72 h shows a significantly better response rate than placebo plus GC in patients with persistent synovitis after at least one failed outpatient intra-articular GC injection.

Introduction

Radiation synovectomy, or radiosynoviorthesis (RSO), has been used for decades. Colloidal particles labelled with β-emitting nuclides are phagocytised by synoviocytes with a uniform distribution in the synovium [1].

Radiation of the synovium causes necrosis and inhibits cell proliferation. Therefore, synovitis can be halted temporarily [2]. Satisfactory control of synovitis is achieved in 40–80% of patients after 1 year, with a decline in symptom control over time [3–8]. Following up on some double-blind studies in the late 1970s, revived interest in RSO has recently resulted in new prospective studies including three randomised, controlled, multicentre studies [9–16]. The clinical efficacy of RSO in these new studies was about 70%, which is comparable with the results of a meta-analysis including 2,190 treated joints and of a prospective, randomised, controlled study conducted in the 1990s [17, 18].

Most studies on radiation synovectomy focus on the knee. RSO of other joints is less frequently studied. The present trial was conducted on cases of synovitis in joints of the upper extremity that persisted despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs), diseasemodifying anti-rheumatic drugs (DMARDs) and at least one intra-articular glucocorticoid (GC) injection without immobilisation at the outpatient department. The objective of the study was to compare the clinical efficacy of RSO plus GC with that of placebo plus GC.

Materials and methods

Patients

Upon referral by their rheumatologists, patients who met the selection criteria and provided informed consent were enrolled from September 1999 until December 2003.

Inclusion criteria were therapy-resistant, persistent synovitis despite at least one intra-articular GC injection in the affected joint, informed consent and mental capacity. Exclusion criteria were age less than 20 years, pregnancy or lactation, and females of reproductive age who wished to bear children or lacked appropriate contraceptive measures.

The following data were recorded: gender, age, diagnosis, disease duration, current therapy, duration of synovitis, type of joint and Steinbrocker radiological criteria [19].

Study design

The study was a randomised, double-blind, placebo-controlled, single-centre, single-observer clinical trial comparing the clinical efficacy of intra-articular radionuclide plus GC injection with placebo plus GC injection. The duration of the study was 12 months.

Because the patients had already failed to respond to an outpatient intra-articular GC injection, the rheumatologist could apply crossover therapy (placebo plus GC to radionuclide plus GC, or vice versa) after 6 months in cases of worsening synovitis, or after 12 months in cases of recurrence of synovitis. The medical ethics committee approved the study protocol.

Randomisation of therapy

Patients were randomly allocated to one of the following treatment groups: (A) intra-articular radionuclide (^{169}Er or ^{186}Re; Shering CIS bio international, France) plus triamcinolone acetonide (Kenacort; Bristol-Meyers Squibb BV, The Netherlands) or (B) placebo plus triamcinolone acetonide. The radionuclide dose and type [as advised by the European Association of Nuclear Medicine (EANM)] and the triamcinolone acetonide dose for each of the different joints are described in Table 1 [20].

Table 1: radioisotope and triamcinolone acetonide (GC) doses for joints of the upper extremity

Joint	^{169}Erbium (MBq)	^{186}Rhenium (MBq)	Triamcinolone acetonide (mg)
Gleno-humeral joint		110	40
Elbow		75	40
Radio-carpal		75	12
Metacarpophalangeal	40		8
Proximal interphalangeal	20		4

Patients randomized to the radiation synovectomy group were injected with the radioisotope plus GC, and patients randomized to the placebo group were injected with placebo plus GC.

Four sets of 20 envelopes, each containing ten group A and ten group B designations, were prepared by the secretary of the Department of Nuclear Medicine. After enrolment of each patient in the study, the same secretary drew an envelope and planned the intra-articular injection for that patient. The patient, first author, principal investigator, other nuclear physicians and rheumatologists were all blinded. In cases of cross-over therapy after 6 or 12 months, only the rheumatologist knew the code. The procedure for administration of cross-over therapy was exactly the same as for randomised therapy.

Injection procedure

One rheumatologist (J.D.M.) administered the injections. Puncture of the joint was performed under sterile conditions and intra-articular needle placement was confirmed by arthrography. If possible, synovial fluid was aspirated. After administration of radionuclide plus GC or placebo plus GC, the needle was flushed with saline to prevent leakage through the needle tract. Following treatment, the injected joint was immobilised with a plaster splint for 72 h.

Clinical assessment

In the literature there is no consensus concerning appropriate outcome measures for assessing the clinical efficacy of RSO.

Therefore, we used a change composite index (CCI) that we utilised previously [14, 16]. The CCI and all other data were collected by a single observer, the main investigator (F.M.v.d.Z.), at baseline and at 6 and 12 months after intra-articular injection. To investigate side-effects, at all visits the patients were asked to report any unusual complaints or symptoms.

Change composite index

To evaluate clinical efficacy, a CCI was calculated using the changes in six clinical variables over time. Acute phase reactants (ESR and CRP levels) were not included in the CCI because patients with oligo-arthritis were treated; thus these variables could have been influenced by arthritis of other joints.

The six variables in the CCI were the following:

1. A functional disability score of the treated joint, assessed by the main investigator based on the complaints of the patient: 0 (no complaints)–3 (severe disability of the affected joint)
2. A visual analogue scale (VAS) of pain for the treated joint, assessed by the patient: 0 mm (no pain)–100 mm (maximal pain)
3. Joint tenderness at palpation of the affected joint: 0 (no tenderness)–3 (wincing/withdrawal upon palpation)
4. Joint swelling, assessed by F.M.v.d.Z.: 0 (no swelling)–3 (major swelling)
5. Patient's global assessment of the effect of therapy: 0 (no improvement or worsening)–3 (strong improvement)
6. Physician's global assessment of the effect of therapy: 0 (no improvement or worsening)–3 (strong improvement)

For the first four variables, the change from baseline was analysed, while for the last two variables the scores at 6 and 12 months were used. Each of the clinical variables could add 0–2 points to the CCI. Improvement of the VAS by <30 mm added 0 points, by 30–50 mm added 1 point and by ≥50 mm added 2 points.

The other variables added 1 point for a 1-point improvement (25– 50%) and 2 points for a 2- or 3-point improvement (50–100%).

Therefore, CCI (secondary outcome) could range from 0 (failure) to 12 (maximal effect). Values are expressed as the mean ± standard deviation (SD). Treatment was considered successful if CCI ≥6, whereas CCI <6 indicated treatment failure; this response rate was the primary outcome.

Concurrent medication

Concurrent medication with oral GC, NSAIDs or DMARDs was permitted. During the study period, changes in concurrent medication were restricted as much as possible. Nevertheless, if changes were necessary because of disease activity in joints other than the treated joint, this information was recorded.

Statistical analysis

Power analysis on the primary outcome measure (response rate) indicated that with an alpha of 0.05, 32 patients would be needed in each group to detect a statistically significant difference between success rates of 70% for radionuclide plus GC versus 40% for placebo plus GC at 6 months with a power of 0.80. Fisher's Exact tests were used to test dichotomous parameters such as response rate. Between groups, differences in mean CCI (secondary outcome) were tested for significance with two-sided, two-sample t tests or Mann- Whitney U tests, when appropriate. The relationship between baseline characteristics and CCI was evaluated by Spearman correlation coefficient. Regression analyses (CCI as the dependent variable in linear regression analyses; treatment success or failure as the dependent variable in logistic regression analyses) were performed to investigate whether baseline variables (independent variables) could predict therapeutic effect. All tests were two-sided; p values ≤0.05 were considered statistically significant. Analyses were performed with Statistical Package for Social Sciences version 11.5.

Results

Baseline characteristics

Sixty-eight intra-articular injections in 44 patients (23 female and 21 male) were administered, 37 with radionuclide plus GC (group A) and 31 with placebo plus GC (group B). At the time of the intra-articular treatments, the mean±SD age of the patients was 59±13 years for group A and 59±13 years for group B. The baseline characteristics of the joints of the two groups are listed in Table 2. No statistically significant differences between groups A and B were found. The predominant diagnosis was rheumatoid arthritis (RA): 73% of patients

in group A and 71% in group B. Psoriatic arthritis was diagnosed in 11% of patients in group A versus 16% in group B, and oligoarthritis e causa ignota (of unknown origin; e.c.i.) was diagnosed in 16% versus 13% of patients in groups A and B, respectively. DMARDs were the most common medication, used by 87% of patients in group A and 81% in group B. Only a few patients with Steinbrocker radiological classification 3 in the affected joint were treated owing to a lower reported success rate for RSO in cases of severe joint damage [5, 21].

In six patients, injected with placebo plus GC, synovitis worsened after 6 months and subsequently the rheumatologist applied radionuclide plus GC. In six other patients, including one patient with two treated joints, synovitis recurred after 12 months. These patients crossed over from placebo plus GC to radionuclide plus GC after 12 months.

No patients crossed over from radionuclide plus GC to placebo plus GC. The mean age of the patients (seven female and five male) at the time of the second intraarticular injection was 61±11 years. The characteristics of the joints prior to cross-over are described in Table 3. One patient who after 12 months crossed over to radionuclide plus GC in a proximal phalangeal joint of the hand, died from cardiac arrest shortly after cross-over treatment.

In ten patients two joints, in seven patients both radiocarpal joints, in one patient both elbows and in two patients two different finger joints were treated simultaneously or within 1 month. In two patients the other radiocarpal joint was treated at least 6 months after the first injection. Consequently, data from 67 treatments, 36 with radionuclide plus GC and 31 with placebo plus GC, could be analysed. The numbers and types of joints treated in groups A and B are described in Table 4.

Table 2: baseline characteristics of all 68 joints

	Group A n=37	Group B n=31
Diagnosis, n (%)		
Rheumatoid arthritis	27 (73)	22 (71)
Psoriatic arthritis	4 (11)	5 (16)
Oligo-arthritis e.c.i.	6 (16)	4 (13)
Disease duration, mean ± SD yr	12 ± 12	9 ± 12
Duration of synovitis, mean ± SD yr	2.3 ± 2.2	1.9 ± 1.8
Steinbrocker radiological classification, n (%) (19)		
Stage 1	17 (46)	16 (52)
Stage 2	15 (41)	14 (45)
Stage 3	5 (13)	1 (3)
Functional disability score, n (%)[a]		
Class 0	0 (0)	0 (0)
Class 1	0 (0)	0 (0)
Class 2	16 (43)	15 (48)
Class 3	21 (57)	16 (52)
Visual analogue scale of pain, mean ± S.D mm	56 ± 25	49 ± 24
Joint tenderness, n (%)[b]		
Class 0	0 (0)	0 (0)
Class 1	0 (0)	0 (0)
Class 2	19 (51)	13 (42)
Class 3	18 (49)	18 (58)
Joint swelling, n (%)[c]		
Class 0	0 (0)	0 (0)
Class 1	7 (23)	3 (10)
Class 2	30 (81)	18 (58)
Class 3	0 (0)	0 (0)

[a] *0 (no complaints) – 3 (severe disability of the affected joint)*

[b] *0 (no tenderness) – 3 (wincing / withdrawal upon palpation)*

[c] *0 (no swelling) – 3 (major swelling)*

There were no significant differences in baseline characteristics between groups A (radioisotope plus GC) and B (placebo plus GC).

Table 3: baseline characteristics of the 13 joints prior to cross-over treatment (from placebo plus GC to radionuclide plus GC; 6 joints after 6 months and 7 joints after 12 months)

	n=13
Diagnosis, n (%)	
Rheumatoid arthritis	10 (77)
Psoriatic arthritis	2 (15)
Oligo-arthritis e.c.i.	1 (8)
Disease duration, mean ± SD yr	13 ± 12
Duration of synovitis, mean ± SD yr	2.8 ± 2.5
Steinbrocker radiological classification, n (%) (19)	
Stage 1	4 (31)
Stage 2	8 (61)
Stage 3	1 (8)
Functional disability score, n (%)[a]	
Class 0	0 (0)
Class 1	0 (0)
Class 2	6 (46)
Class 3	7 (54)
Visual analogue scale of pain mean ± SD mm	60 ± 25
Joint tenderness, n (%)[b]	
Class 0	0 (0)
Class 1	0 (0)
Class 2	5 (38)
Class 3	8 (62)
Joint swelling, n (%)[c]	
Class 0	0 (0)
Class 1	2 (15)
Class 2	11 (85)
Class 3	0 (0)

[a] *0 (no complaints) – 3 (severe disability of the affected joint)*

[b] *0 (no tenderness) – 3 (wincing / withdrawal upon palpation)*

[c] *0 (no swelling) – 3 (major swelling)*

Table 4: distribution of the 67 joints in treatment groups A and B

Joints	Radioisotope plus GC Group A	Placebo plus GC Group B
Radio-carpal joint	20	20
Elbow	8	5
Gleno-humeral joint	2	1
Metacarpophalangeal joint	2	3
Proximalphalangeal joint	5	2

Clinical effect

Radionuclide plus GC versus placebo plus GC

Six months after intra-articular injection, the response rate (CCI ≥6; primary outcome) was 69% (25/36) in group A and 29% (9/31) in group B (p=0.001; Table 5). The mean± SD CCI (secondary outcome) was 6.7±3.2 for group A and 3.3±3.8 for group B (p=0.001). At 12 months the response rate was 69% (25/36) in group A and 32% (8/25) in group B (p=0.004; Table 6). The mean CCI was 6.8±3.3 for group A and 4.2±4.7 for group B (p=0.046).

Table 5: response rates of the 67 treatments, including cross-over treatments, at 6 months

	Radioisotope plus GC Group A	Placebo plus GC Group B
Successful treatment, n (%)	25 (69)	9 (29)
Unsuccessful treatment, n (%)	11 (31)	22 (71)

P=0.001

Table 6: response rates of the 61 treatments, including cross-over treatments, at 12 months

	Radioisotope plus GC Group A	Placebo plus GC Group B
Successful treatment, n (%)	25 (69)	8 (32)
Unsuccessful treatment, n (%)	11 (31)	17 (68)

P=0.004

Six patients crossed over from placebo plus GC to radionuclide plus GC after 6 months. Of these six patients, four (67%) had a successful clinical effect (CCI ≥6) at 6 months after cross-over treatment and three (50%) after 12 months. The mean CCI in these six patients was 7.5±3.8 at 6 months and 5.5±3.9 at 12 months. For the patients who crossed over from placebo plus GC to radionuclide plus GC after 12 months, the response rates were 83% (5/6) at 6 months (mean CCI 7.8±2.4) and 83% (5/6) at 12 months (mean CCI 7.7±2.0). Prior to cross-over, the treatments had a mean CCI of 0.7±1.8 at 6 months.

Four patients, all belonging to group B, changed medication. Three received a higher dose of DMARDs, and one changed from DMARD to NSAID. Two of these patients had CCI ≥6 at both 6 and 12 months.

To exclude the influence of multiple joint treatments in the same patient, 44 randomly chosen injections in the 44 studied patients were analysed. At 6 months the response rates were 70% (16/23 patients; mean CCI 6.8±3.5) for GC plus radionuclide and 29% (6/21 patients; mean CCI 3.4±4.3) for GC plus placebo (p=0.01 for response rate and p=0.007 for mean CCI). At 12 months, the response rates were 70% (16/23 patients; mean CCI 7.1±3.4) for GC plus radionuclide and 41% (7/17 patients; mean CCI 4.9±5.0) for GC plus placebo (p>0.05 for both response rate and mean CCI). In four patients, no data at 12 months were available for the placebo plus GC group owing to crossover to the radionuclide plus GC group after 6 months.

To exclude influence of cross-over treatments only the non-cross-over injections were analysed. At 6 months the response rates were 67% (16/24 patients; mean CCI 6.7±3.4) for GC plus radionuclide and 29% (9/31 patients; mean CCI 3.4±3.8) for GC plus placebo (p=0.007 for response rate and p=0.01 for mean CCI). At 12 months, the response rates were 71% (17/24 patients; mean CCI 7.1±3.3) for GC plus radionuclide and 32% (8/25 patients; mean CCI 4.2±4.7) for GC plus placebo (p=0.01 for response rate and p=0.02 for mean CCI).

RA versus non-RA

To evaluate the response rates according to diagnosis, we categorised the treated joints as either RA or non-RA, since RA joints reportedly respond better to RSO [17]. At 6 months, the success rates for all treatments were 49% (mean CCI 5.0±3.9) for RA and 56% (mean CCI 5.5±3.6) for non-RA. At 12 months, the treatment success rates were 58% (mean CCI 5.9±4.1) for RA and 44% (mean CCI 5.9±4.1) for non-RA. Differences were not significant.

In the placebo plus GC group, response rates at 6 months were 18% (mean CCI 2.5±3.5) for RA and 56% (mean CCI 5.4±3.9) for non-RA. At 12 months, response rates were 22% (mean CCI 3.0±4.4) for RA and 57% (mean CCI 7.3±4.4) for non-RA. The differences in response rates were not statistically significant, but the p values for the differences in mean CCI were 0.048 at 6 months and 0.04 at 12 months.

In the radionuclide plus GC group, the response rates at 6 months were 74% (mean CCI 7.1±3.1) for RA and 56% (mean CCI 5.6±3.6) for non-RA ($p>0.05$). At 12 months the response rates were 81% (mean CCI 7.8±2.7) for RA and 33% (mean CCI 3.9±3.4) for non-RA, with $p=0.01$ and $p=0.001$ for the differences in response rate and mean CCI, respectively.

Steinbrocker radiological classification 1 or 2 versus 3

Owing to a lower reported success rate for RSO in cases of severe joint damage [5, 21], only five joints with Steinbrocker radiological classification 3 were treated. At 6 months, the success rates for all treatments were 52% (mean CCI 5.2±3.8) for Steinbrocker classification 1 or 2 and 40% (mean CCI 4.4±4.8) for Steinbrocker classification 3. At 12 months, the success rates were 54% (mean CCI 5.6±4.2) for Steinbrocker classification 1 or 2 and 60% (mean CCI 7.2±3.0) for classification 3 ($p>0.05$). In the placebo plus GC group, only one joint with Steinbrocker radiological classification 3 was treated. At both 6 and 12 months, the CCI was ≥6. In the radionuclide plus GC group, four joints with Steinbrocker radiological classification 3 were treated. At 6 months, one of these patients (25%) had CCI ≥6 versus 24 of 32 patients (75%) with Steinbrocker classification 1 or 2. At 12 months, two of four patients (50%) with Steinbrocker classification 3 had CCI >6, compared with 23 of 32 patients (72%) with classification 1 or 2. These differences were not statistically significant.

Adverse effects

The patients reported no treatment-related complaints, and no adverse physical effects could be detected at clinical visits.

Prediction of clinical effect

We analysed baseline characteristics and CCIs of joints grouped according to treatment strategy, diagnosis (RA versus non-RA) and cross-over status. No correlations were found between the mean CCI at 6 months and baseline characteristics.

Univariate regression analysis, using the baseline characteristics listed in Table 2 as independent variables, did not yield statistically significant results.

Discussion

RSO has been used in our hospital for more than 15 years to treat patients with persistent synovitis in joints of the upper extremity that is unresponsive to NSAIDs, DMARDs and at least one intra-articular GC injection without immobilisation at the outpatient department. This policy reflects the daily clinical practice in our hospital, whereas the policy in some parts of The Netherlands is to attempt RSO only after two failed outpatient intra-articular GC injections without immobilisation. In this study, our hospital's policy was tested for joints of the upper extremity.

There is no uniform, validated system for scoring the effect of RSO, so comparison with other studies can be difficult. The CCI method has been used previously [14, 16]. The clinical outcome of our study is comparable to a meta-analysis by Kresnik et al. in which clinically relevant improvement occurred in 73%±17% of patients treated with RSO [17]. The results of our study are also comparable to the results of a prospective study using the same method [14]. The effect rate in that study was 68% at 12 months for a mixture of upper and lower extremity joints; the effect rate for the upper extremity joints was 79% and for the lower extremity joints, 60% [14]. This result confirms our experience: the effect rate of RSO is higher for upper extremity than for lower extremity joints.

We believe that mechanical forces in weight-bearing joints are greater than in non-weight-bearing joints. Such forces could perpetuate joint damage and influence the recurrence of synovitis. These hypotheses could at least partly explain the discrepancy between our results and those of the Dutch multicentre trial of RSO in the knee joint. In the Dutch multicentre trial, the response rates for placebo plus GC and for radionuclide plus GC were both about 50% [16].

Another explanation for differences with the Dutch multicentre trial could be the selection of patients. In our study, patients were enrolled after one failed intra-articular GC injection without immobilisation at the outpatient department, whereas in the Dutch multicentre trial, patients were enrolled after two failures. Thus, the tendency for recurrence of synovitis could have been higher in the patients selected for the Dutch multicentre trial.

The treatment of more than one joint in the same patient could be considered a disadvantage of our study. Therefore, we randomly selected 44 treatments in 44 patients. At 6 months the response rate for RSO plus GC (70%) was significantly higher than that for placebo plus GC (29%).

However, at 12 months there was no significant difference in response rate between the two groups. An explanation for this result is that at 12 months there were no data for four

treatments in the placebo plus GC group owing to treatment failure and subsequent cross-over to RSO.

The time period for clinical assessment of the effect of RSO is debatable. In the study of Sledge and co-workers, 6 months was regarded as adequate for clinical assessment because of the lag phase in the effect of irradiation by radionuclides [22]. Similarly, in the multicentre trial by Jahangier et al., clinical assessment after 6 months seemed justified [16]. In our study, the clinical effect of treatment was also measured at 12 months. We found that the effect rates at 12 months were comparable. Tebib and co-workers described a higher recurrence rate in the second year for intra-articular GC than for RSO [13]. In two earlier retrospective studies, we observed a decline in the effect of RSO over time, especially after 12–24 months, but these studies focussed on the knee and ankle joints [7, 21].

In the present study, patients reported no adverse effects. In contrast, the study by Tebib and co-workers documented adverse events in up to 30% of patients [13]. These adverse effects were mainly transient pain or swelling, and in one patient a facial rash, lasting for 12 h [13]. In the study by Kahan et al., transient pain or swelling was described in 5% of patients in the radionuclide group and in 7% of the placebo group [12]. In neither study were skin or needle tract burns by back-flushing of the radionuclide through the needle tract reported. In the Dutch multicentre study of the knee, adverse effects were described in 6% of patients in the radionuclide plus GC group and in 1% of patients in the placebo plus GC group [16]. A possible explanation for the differences with our study is the method used to investigate adverse effects. In our study, the treated joints were not physically examined within the first week of injection. In addition, there might be a discrepancy among the studies in the definition of adverse effects.

In the literature a less favourable outcome for RSO has been reported in more severely damaged joints [5, 17, 21, 23] and in diseases other than RA, especially osteoarthritis [5]. In our study, no significant differences between Steinbrocker radiological classification 1 or 2 and Steinbrocker classification 3 were found. However, the number of treated joints (five) with Steinbrocker radiological classification 3 was too small to draw valid conclusions.

In our study, the non-RA joints in the placebo plus GC group showed a significantly higher mean CCI at 6 and 12 months, yet there was no significant difference in response rates. In the radionuclide plus GC group, there were no significant differences at 6 months. However, at 12 months the difference in response rates (81% for RA versus 33% for non-RA) was significant.

In conclusion, RSO (radionuclide plus GC) of upper extremity joints with immobilisation for 72 h shows a significantly better response rate than placebo plus GC in patients with persistent synovitis after at least one failed outpatient intra-articular GC injection. Therefore, we recommend RSO in patients in whom the disease as a whole is fairly well controlled with only one or at most a few joints resistant to systemic therapy and one outpatient intra-articular GC injection. The indication is similar to that for surgical synovectomy, which can still be

tried in the event of an RSO failure. Although in theory any joint of the upper extremity could be injected, in our practice injection is restricted to the glenohumeral joint, the elbow, and the radiocarpal, metacarpophalangeal and proximal interphalangeal joints.

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Chapter 4

Radiation synovectomy of the upper extremity joints: does leakage from the joint to non-target organs impair its therapeutic effect?

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Abstract

Does leakage impair the therapeutic effect of radiosynoviorthesis (RSO)? Are there differences in leakage between Erbium and ^{186}Rhenium?

At baseline and at 6 and 12 months after RSO, six clinical parameters were scored. Changes in clinical variables over time were summed to a change composite index (CCI), ranging from 0 (no effect) to 12 (maximal effect). CCI ≥ 6 was considered successful treatment. Differences in leakage between responders and non-responders, and between ^{169}Erbium and ^{186}Rhenium were examined.

Regression analyses were performed to explore whether baseline variables predicted leakage.

Both at 6 and 12 months response rates were 25 of 36 (69%). Five of 11 (45%) non-responders showed leakage versus 20 of 25 (80%) responders (P = 0.06). Mean leakage to lymph nodes was 0.4±0.7% versus 2.4±0.8% (P = 0.04). Median leakage to liver/spleen was 0% versus 0.3% (P = 0.4). Only age at the time of injection correlated significantly with leakage to lymph nodes. The ^{169}Erbium group showed leakage in 1 of 7 (14%) versus 24 of 30 (80%) for the ^{186}Rhenium group (P = 0.002). Mean leakage to lymph nodes was 0.11±0.3% versus 2.1±2.8% (P = 0.001). Median leakage to liver/spleen was 0% versus 0.5% (P = 0.006).

Leakage to non-target organs does not impair the clinical effect of RSO. Only age predicted leakage to lymph nodes significantly. Other baseline characteristics did not predict leakage. ^{169}Erbium shows significantly lower leakage to non-target organs than ^{186}Rhenium in RSO.

1. Introduction

Chronic rheumatic synovitis resistant to nonsteroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs (DMARDs), and intraarticular glucocorticoid (GC) injection may be controlled with synovectomy. Three types of synovectomy are known: chemical, surgical or radiation.

Chemical synovectomy with osmic acid was first described in 1951 (Von Reiss and Swensson, 1951). Osmic acid is an aqueous solution of osmium tetroxide, which is a vigorous oxidizing agent. It is deposited in inflamed synovial tissue and synovial fat, inducing necrosis of the inflamed synovial membrane. The results of chemical synovectomy are variable, but satisfactory disease control can be achieved (Sheppeard and Ward, 1980; Nissila et al., 1977; Oka et al., 1969). In a more recent retrospective study, response rates at 6 and 12 months of 67% and 50% are described, declining to 18% at 36 months (Bessant et al., 2003). The use of chemical synovectomy is limited to knee joints; to our knowledge there is no literature of chemical synovectomy in other joints.

Surgical synovectomy has evolved from open to arthroscopic techniques. Surgical synovectomy is successful in 40–90% of treated patients. The duration of remission varies from a relatively short period up to many years (Shibata et al., 1986; Akagi et al., 1997; McEwen, 1988; Jensen et al., 1991; Roch-Bras et al., 2002). In contrast to chemical synovectomy, surgical synovectomy has also been studied in upper extremity joints (Nemoto et al., 2004; Nakamura et al., 2004).

Radiation synovectomy or radiosynoviorthesis (RSO) was first described in 1952 (Fellinger and Schmid, 1952). The intraarticular injected small particles labeled with ß-emitting isotopes are phagocytized by macrophagelike synoviocytes and other phagocytizing inflammatory cells in the subsynovial connective tissue (Ingrand, 1973).

Radiation of the synovium causes necrosis and inhibits cell proliferation. Therefore, synovitis can be halted temporarily (Meier-Ruge et al., 1976). In a meta-analysis, clinically relevant improvement in 73 ± 17% (mean ± standard deviation (SD) of patients treated with RSO is described (Kresnik et al., 2002). A placebo-controlled double-blind study of knee joints reported response rates of 48% at 6 months, decreasing to 44% at 18 months (Jahangier et al., 2005). In a prospective multicenter study, a relapse-free interval of 24 months was achieved in 70% of RSOs with ^{186}Rhenium (Tebib et al., 2004).

Leakage from the treated joint is a drawback of RSO, which can lead to radiation of non-target organs. Leakage of up to 48% of the administered dose to lymph nodes has been described for the formerly used radioactive gold particles (Virkkunen et al., 1967; Topp et al., 1975; Correns et al., 1969). For the newer ^{165}Dysprosium hydroxide macroaggregate the maximal, reported leakage is 9% (Zalutsky et al., 1986). The European Association of Nuclear Medicine (EANM) advises ^{90}Yttrium-, ^{169}Erbiuim- and ^{186}Rhenium-colloids for RSO (Clunie

et al., 2003). In our experience, leakage to non-target organs for these radiopharmaceuticals is small. However, leakage of 70% has been described in RSO with ^{90}Yttrium (Gedik et al., 2004). Leakage of ^{169}Erbiuim is small (Gratz et al., 1999). The maximal leakage for ^{186}Rhenium colloids is 9.5% (van der Zant et al., 2004). The effect of leakage on the clinical efficacy of RSO has not been studied.

The primary aim of this study was to investigate the impact of leakage to non-target organs on the clinical outcome of RSO of upper extremity joints. Secondary aims were to investigate whether clinical baseline variables or patient characteristics could predict leakage and to examine the differences in leakage between ^{169}Erbium and ^{186}Rhenium. Furthermore, the radiation doses to the leakage organs were estimated.

2. Patients and methods

Upon referral by their rheumatologists, patients who met the selection criteria and provided informed consent were enrolled from September 1999 until December 2003. Inclusion criteria were therapy-resistant, persistent synovitis despite at least one intraarticular GC injection in the affected joint; informed consent; and mental capacity. Exclusion criteria were age less than 20 years; pregnancy or lactation; and females of reproductive age who wished to bear children or lacked appropriate contraceptive measures.

The following data were recorded: gender, age, diagnosis, disease duration, current therapy, duration of synovitis, type of joint, and Steinbrocker radiological stage (Steinbrocker et al., 1949).

2.1. Clinical assessment

In the literature, there is no consensus concerning appropriate outcome measures for assessing the clinical efficacy of RSO. Therefore, we used a change composite index (CCI) that we utilized previously (Jahangier et al., 2001, 2005; van der Zant et al., 2004). The CCI and all other data were collected by the main investigator (FMvdZ) at baseline and at 6 and 12 months after intraarticular injection. The CCI was calculated using the changes in six clinical variables over time. Acute phase reactants (ESR and CRP levels) were not included in the CCI because patients with oligo-arthritis were treated; thus these variables could be influenced by arthritis of other joints.

The six variables in the CCI were the following:

1. A functional disability score of the treated joint based on the complaints of the patient: 0 (no

complaints)—3 (severe disability of the affected joint).
2. A visual analog scale (VAS) of pain for the treated joint, assessed by the patient: 0mm (no pain)—100mm (maximal pain).
3. Joint tenderness at palpation of the affected joint: 0 (no tenderness)—3 (wincing/withdrawal upon palpation).
4. Joint swelling: 0 (no swelling)—3 (major swelling).
5. Patient's global assessment of the effect of therapy: 0 (no improvement or worsening)—3 (strong improvement).
6. Physician's global assessment of the effect of therapy: 0 (no improvement or worsening)—3 (strong improvement). For the first four variables, the change from baseline was analyzed; while for the last two variables, the scores at 6 and 12 months were used. Each of the clinical variables could add 0–2 points to the CCI. Improvement of the VAS < 30mm added 0 points, 30–50mm added 1 point, and ≥ 50mm added 2 points. The other variables added 1 point for a 1-point improvement (25–50%) and 2 points for a 2- or 3-point improvement (50–100%). Therefore, CCI could range from 0 (failure) to 12 (maximal effect). Values are expressed as the mean ± SD. Patients were considered as responders if CCI ≥ 6, whereas CCI < 6 were considered as non-responders.

2.2. Concurrent medication

Concurrent medication with oral GC, NSAIDs or DMARDs was continued. During the study period, changes in concurrent medication were restricted as much as possible. Nevertheless, if changes were necessary because of disease activity in joints other than the treated joint, this information was recorded.

2.3. Injection procedure

One rheumatologist (JDM) administrated the injections. Paracenthesis of the joint was performed under sterile conditions and intraarticular needle placement was confirmed by arthrography (ultravist 300, Schering AG Berlin, Germany). If possible, synovial fluid was aspirated. After administration of radioisotope (^{169}Erbium or ^{186}Rhenium; Schering CIS bio international, France) and triamcinolone acetonide (Kenacort®, Bristol-Meyers Squibb BV, The Netherlands), the needle was flushed with saline to prevent leakage through the needle tract. The radioisotope dose [as advised by the EANM] and the triamcinolone acetonide dose for each joint are described in Table 1 (Clunie et al., 2003). Following treatment, the injected joint was immobilized with a plaster splint for 72 h.

Table 1: radioisotope and triamcinolone acetonide (GC) doses for joints of the upper extremity

Joint	^{169}Erbium (MBq)	^{186}Rhenium (MBq)	Triamcinolone acetonide (mg)
Shoulder		110	40
Elbow		75	40
Radio-carpal		75	12
Metacarpophalangeal	40		8
Proximal interphalangeal	20		4

MBq=Megabecquerel
mg=milligram

2.4. Leakage measurements

About 24 h after the injection, leakage of the radionuclide was measured with a single-head gamma camera.

Views of the treated joint, regional lymph nodes and liver/ spleen were obtained with the following acquisition variables; for ^{186}Rhenium: time 150 s, energy peak; peak 1: 140 keV with a window of 15%, peak 2: 62 keV with a window of 20% (for measuring Brehmmstrahlung), matrix 256 x 256 and for ^{169}Erbium: time 300 s, energy peak 50 keV with a window of 100% (for measuring Brehmmstrahlung), matrix 256 x 256. Regions of interest (ROI) were drawn around target areas and background areas.

Leakage was expressed as counts in the target ROI corrected for background relative to total counts corresponding with percentage of injected dose.

2.5. Dosimetry

For radiation synovectomy, the dose D_{syn} in the synovium can be determined using the equation:

$$D_{syn} = \frac{A_{syn} F}{\lambda_n S_{syn}} \quad (1)$$

where A_{syn} is the total activity in the synovium, λ_n the nuclear decay constant of the radionuclide and F is for the absorbed dose constant (in Gy cm^2MBq^{-1} s^{-1}) (Johnson et al., 1995). S_{syn} (surface of the synovium in cm2) is 85 for shoulder, 60 for elbow, 31 for radiocarpal joint, 10 for metacarpophalangeal joint and 5 for proximal interphalangeal joint (Mens, 1987).

Given the distribution of the radionuclide in the body, it is possible to calculate the dose to the whole body as well as to different organs.

The tissue penetration of β-radiation (electrons) is within the range of millimeters. Assuming that organs are bigger than the average range of electrons, the dose is given by:

$$D_{org}^{\beta} = 1.6 * 10^{-10} \frac{A_{org}}{\lambda_{eff}} \frac{\sum y_i E_i}{m_{org}} \quad (2)$$

in which A_{org} stands for the total activity in the organ, y_i is fraction of energy, E_i in the decay spectrum and m_{org} is the mass of the organ. The effective decay constant $l_{eff} = l_n + l_{bio}$; l_n is the nuclear decay constant and l_{biol} is the biological decay constant.

As the diameter of a lymph, node is within the (average) range of an emitted electron, a correction is necessary. Assuming that continuous slowing down approximation holds, the fraction of the dose deposited in a small organ follows from

$$D_{lymph}^{\beta} = D_{org}^{\beta} \frac{r_{lymph}}{r_{avg}^{\beta}} \quad (3)$$

with r_{lymph} the (average) radius of the lymph node. The for ^{186}Re is about 1.2mm and the for ^{169}Er is about 0.3 mm.

As ^{186}Re emits β- and γ-radiation, both should be considered separately. ^{186}Re has two γ-photons with energies of 137 keV (8.6% of the disintegrations) and 123 keV (1.8% of the disintegrations) (ICRP, 1983). γ-photons have much less tissue absorption compared to β-radiation. So, the contribution of γ-radiation to organ dose is small and will be neglected. For ^{169}Er, only β-radiation has to be considered.

2.6. Statistical analysis

Fisher's exact tests were used to test dichotomous parameters, such as leakage yes or no. Between groups, differences in mean values were tested for statistical differences with

two-sided, two-sample *t*-tests, ANOVA tests or Mann–Whitney *U*-tests, when appropriate. The relationship between baseline characteristics and leakage was evaluated by Spearman correlation coefficient. Regression analyses (lymph node leakage or liver/spleen leakage as dependent variable) were performed to investigate whether baseline variables (independent variables) could predict leakage. All tests were two-sided; *P*-values ≤0.05 were considered statistically significant. Analyses were performed with Statistical Package for Social Sciences (SPSS) version 11.5.

3. Results

Thirty-seven RSOs (2 shoulders, 8 elbows, 20 radiocarpal joints, 2 metacarpophalangeal III joints, 3 proximal interphalangel III joints, 1 proximal interphalangel II joint and 1 proximal interphalangel IV joint) in 31 patients (mean age 59±13, range 25–84) were performed. The baseline characteristics of the treated joints are listed in Table 2. One patient died from non-RSO-related cardiac arrest shortly after RSO. Consequently, data of 36 RSOs could be analyzed.

The response rate was 25 of the 36 (69%) at 6 months, with a mean CCI of 6.7 ± 3.2 and 25 of 36 (69%) at 12 months with a mean CCI of 6.8 ± 3.3.

In 25 of 37 (68%) treatments, there was leakage to lymph nodes and/or liver/spleen, and in 12 there was no leakage at all. In 17 both leakage to lymph nodes and liver/spleen was seen, in 6 only leakage to lymph nodes and in 2 only leakage to liver/spleen was observed. The mean leakage to the lymph nodes was 1.7 ± 2.7% (range 0–9.9%). The median for leakage to liver/spleen was 0.2% (range 0–6.8%).

Leakage occurred in 5 of 11 (45%) RSOs with a CCI < 6 at 6 months and in 20 of 25 (80%) RSOs with a CCI ≥ 6 at 6 months ($P = 0.06$). In 11 non-responders, mean leakage to the lymph nodes was 0.4 ± 0.7% versus 2.4 ± 0.8% in 25 responders ($P = 0.03$). The median leakage for liver/spleen was 0% for non-responders and 0.3% for responders ($P = 0.4$).

In 23 of the RSOs the underlying disease was RA and in 14 non-RA.Mean leakage to lymph was 2.3 ± 3.1% for RA and 0.9 ± 1.3% for non-RA ($P = 0.07$). For liver/spleen leakage, median was 0.5% for RA and 0% for non-RA ($P = 0.06$).

For Steinbrocker radiological classes 1, 2 and 3, the mean leakage ± SD to lymph nodes was 3.0 ± 3.3%, 0.8 ± 1.6% and 1.7 ± 0.7% ($P = 0.03$), respectively and Mean ± SD liver/spleen leakage was 0.7 ± 1.6%, 1.1 ± 1.6% and 0.2 ± 0.5% ($P = 0.6$), respectively. When Steinbrocker radiological classification was dichitomized according to 1 or 2 versus 3, no significant differences in mean leakage to lymph nodes ($P = 0.07$), or leakage to liver/spleen ($P = 0.4$) was found.

^{169}Erbium was administrated in 7 RSOs and ^{186}Rhenium in 30 RSOs. In the ^{169}Erbium

group only in 1 of 7 (14%) treatments leakage was observed, versus 24 of 30 (80%) in the ^{186}Rhenium group ($P = 0.002$). Mean leakage to the lymph nodes was for ^{169}Erbium 0.11 ± 0.3% and for ^{186}Rhenium 2.1 ± 2.8% ($P = 0.001$). The median for leakage to liver/spleen was 0% for ^{169}Erbium and 0.5% for ^{186}Rhenium ($P = 0.006$).

Table 2: baseline characteristics of 37 treated joints in 31 patients

	n=37
Diagnosis, n (%)	
Rheumatoid arthritis	27 (73)
Psoriatic arthritis	4 (11)
Oligo arthritis e.c.i.	6 (16)
Disease duration, mean ± S.D yr	12 ± 12
Duration of synovitis of the treated joint, mean ± S.D yr	2.3 ± 2.2
Steinbrocker radiological class, n (%) (19)	
1	17 (46)
2	15 (41)
3	5 (13)
Functional disability score, n (%)[a]	
0	0 (0)
1	0 (0)
2	16 (43)
3	21 (57)
Visual analogue scale of pain mean in mm ± S.D	56 ± 25
Joint tenderness, n (%)[b]	
0	0 (0)
1	0 (0)
2	19 (51)
3	18 (49)
Joint swelling, n (%)[c]	
0	0 (0)
1	7 (23)
2	30 (81)
3	0 (0)

[a] *0 (no complaints) – 3 (severe disability of the affected joint)*

[b] *0 (no tenderness) – 3 (wincing / withdrawal upon palpation)*

[c] *0 (no swelling) – 3 (major swelling)*

3.1. Prediction of leakage

When baseline characteristics; age at the time of injection, disease (RA versus non-RA), disease duration, duration of synovitis, gender, functional disability score, VAS, joint tenderness, Steinbrocker radiological classification (1 or 2 versus 3) and joint swelling were correlated with lymph node leakage and liver/spleen leakage, only for age at the time of injection the correlation with leakage to lymph node was significant (r = -0.58, P = 0.0001).

Regression analyses showed that age at the time of injection could significantly predict lymph node leakage (r = -0.6, P = 0.0001). The other baseline characteristics could not significantly predict leakage to lymph nodes or leakage to liver/spleen.

3.2. Dosimetry to the synovium and leakage organs

In Table 3, the doses to the synovium for each kind of joint are described, using Eq. (1). Using Eqs. (2) and (3), the maximal dose to lymph node was 86 Gray (Gy) in ^{186}Rhenium RSO of a radio-carpal joint with leakage to lymph node of 9.9%. In ^{169}Erbium RSO of a metacarpophalangeal joint with leakage of 0.8% maximal dose to lymph node was 3.0 Gy. The maximal dose to liver/ spleen was 0.012 Gy to the liver/spleen in ^{186}Rhenium RSO of a radio-carpal joint with leakage of 6.8% to liver/ spleen. In RSO with ^{169}Erbium, there was no leakage to liver/spleen.

Table 3: the doses to the synovium for each joint

Joint	Joint surface (cm2)	Nuclide	Activity (MBq)	Dose to the synovium (Gy)
Shoulder	85	^{186}Rhenium	110	2.3
Elbow	60	^{186}Rhenium	75	2.2
Radio-carpal	31	^{186}Rhenium	75	4.3
Metacarpophangeal	10	^{169}Erbium	40	9.0
Proximal interphalangeal	5	^{169}Erbium	20	9.0

MBq=Megabecquerel
Gy=Gray

4. Discussion

In literature, the effect of leakage to non-target organs on the response rate of RSO has scarcely studied. In this study, leakage to lymph nodes and/or liver/spleen did not impair clinical effect of RSO. The mean leakage to lymph nodes was even significantly higher in responders, for which is no clear explanation.

Theoretically, the following factors can increase leakage: (1) mobilization of the joint; (2) intraarticular hydrostatic pressure caused by synovial fluid; (3) injection technique; (4) the grade of inflammation representing hypervascularity; (5) the interference of X-ray contrast with the radiopharmaceuticals, especially ethylenediaminetetraacetic acid (EDTA). EDTA can chelate radiocolloids and the dissolved radionuclide can leak more easily than the bound radiocolloids; (6) the particle size of the colloids.

Immobilization is beneficial for the clinical effect and can lower leakage (Gratz et al., 1999). Therefore, in our institution the joints are immobilized with a plaster splint for 72 h. The influence of hydrostatic pressure within the joint on leakage has not been studied. But it seems common sense to lower the intraarticular pressure by aspiration of as much as possible synovial fluid before administration of the radiocolloids plus GC. Also an adequate, low traumatizing injection technique could lower leakage rate.

Theoretically, the grade of hypervascularity and/or hyperpermeability could influence leakage especially if the radiocolloids are chelated. The small radionuclide can enter the bloodstream more easily. By adding GC to the radiocolloids in RSO, hypervascularity as consequence of inflammation can be diminished and so leakage can be inhibited. Only one study concluded co-injection of GC might not be necessary, although this was a study of RSO of the knee in hemophilic patients (Gedik et al., 2004). No studies have been performed in which leakage was compared in RSO with or without co-administration of GC. In our institution, GC is almost always co-administered because besides this theoretical benefit on leakage, GC can bridge the lag phase from the moment of injection to the moment of the effect of RSO and can lower the risk of radiation-induced synovitis.

Interference of GC, X-ray contrast and anesthetics on the stability of radiocolloids has been studied in vitro. EDTA containing X-ray contrast could mobilize 5–20% of ^{169}Erbium and ^{90}Yttrium out of the colloids, but triamcinolone did not have effect on stability in the presence of synovial fluid (Schoma¨ cker et al., 2005). However, Franssen et al. (1997) did not find significant differences in excretion of ^{90}Yttrium via the urine after RSO using contrast agents with or without EDTA in vivo.

In our opinion, particle size of the colloids is, next to immobilization, the most important factor in leakage. The appropriate size is considered to be 2000–5000 nm (Noble et al., 1983). In Europe, three radiocolloids for RSO are commercially available. The size of colloidal ^{186}Rheniumsulfide is 50–300 nm, of ^{90}Yttrium colloid 200nm and of ^{169}Erbium

2000–3000 nm (Shering CIS bio international, France), or 100 nm for ^{90}Yttrium colloid (GE Amersham Healthcare). Radioactive gold particles of 20nm did show leakage to lymph nodes in 30% of the treatments, whereas particles of 300nm did not show any leakage to lymph nodes (Virkkunen et al., 1967; Topp et al., 1975; Correns et al., 1969; Topp and Cross, 1970). Maximal leakage up to 48% of the injected dose to lymph nodes has been described, although the smallest particles were not designed for radiation synovectomy (Virkkunen et al., 1967), and leakage of 70% of the injected dose for ^{90}Yttrium (Gedik et al., 2004). In some studies, other agents not commercially available with larger particle sizes than the above mentioned have been used. Maximal leakage varied from 3% of the injected dose for ^{153}Samarium hydroxyapatite, with particle sizes of 1600–2200 nm, to 9% of the injected dose for ^{165}Dysprosium hydroxide macroaggregate, with particle sizes of 2000–5000 nm (Clunie et al., 1995; Zalutsky et al., 1986). In another study with ^{166}Holmiun polymeric microspheres (particle sizes of 2000–13,000 nm) minimal retention in the joint was 95% of the injected dose, i.e. leakage to non-target organs was less than 5% (Umper et al., 1992).

In our study there was leakage in only 1 out of 7 (14%) RSOs with ^{169}Erbium compared to 24 out of 30 (80%) for ^{186}Rhenium. Also mean leakage to lymph nodes and/or liver/spleen was significantly lower for ^{169}Erbium. In our opinion, the difference in particle size of the colloids, with a favorite particle size for ^{169}Erbium of 2000–3000 nm, is the major part of the explanation for this difference. Maximal lymph node dose for ^{169}Erbium was 3.0 Gy versus 86 Gy for ^{186}Rhenium and liver/spleen dose was 0 Gy for ^{169}Erbium versus 0.012 Gy for ^{186}Rhenium. Only age at the time of injection could predict leakage.

We found a negative correlation. In literature, there is no explanation for this; decline of lymphatic transport capacity with aging might be an explanation. The difference in leakage to lymph nodes between radiological classes 1, 2 versus 3 is explained by 3 young patients with high leakage to lymph nodes, ranging from 6.5% to 9.9% in radiological class 1.

5. Conclusion

Leakage to non-target organs, lymph nodes and/or liver/ spleen, does not negatively influence the effect of RSO of the upper extremity joints. Only age at the time of injection could predict leakage; higher leakage in younger patients. ^{169}Erbium shows a significantly lower leakage to non-target organs than ^{186}Rhenium in RSO of the upper extremity joints.

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Chapter 5

The intra-articular distribution of ^{90}Yttrium does not influence the clinical outcome of radiation synovectomy of the knee

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Abstract

Objectives

To assess the impact of the intra-articular distribution of ^{90}Yttrium-citrate (^{90}Y) on the clinical effect of radiosynoviorthesis (RSO) of the knee and on ^{90}Y leakage from this joint.

Methods

Patients with arthritis of the knee received 185 MBq ^{90}Y combined with a glucocorticoid, followed by clinical bed rest. Intra-articular ^{90}Y distribution, measured with a dual-head gamma camera immediately or after 24 hours, was scored as mainly diffuse or mainly focal. Leakage to regional lymph nodes, the liver and spleen was assessed with a dual-head gamma camera after 24 hours. Clinical effect was scored after 6 months by a composite change index (CCI), range 0–12; responders were defined as having a CCI ≥6.

Results

Seventy-eight knees of 69 patients, mostly suffering from undifferentiated arthritis (42%) or RA (28%), were treated. ^{90}Y distribution was mainly diffuse in 54% and mainly focal in 46% with clinical response rates of 40% versus 56%, respectively, $p = 0.3$. CCI was not correlated with distribution. ^{90}Y leakage was found only to the liver and the spleen (mean leakage 0.4% and 1.1%, respectively). Leakage was significantly less in case of diffuse intra-articular ^{90}Y distribution, whereas leakage to the liver was correlated with distribution ($r = 0.68$, $p<0.001$). ^{90}Y leakage was not correlated with CCI.

Conclusions

Intra-articular ^{90}Y distribution does not influence the clinical effect of RSO of the knee. Although ^{90}Y leakage from the joint is less if ^{90}Y distributes diffusely in the joint cavity, leakage does not seem to hamper the clinical effect.

Radiation synovectomy or radiosynoviorthesis (RSO) is a therapeutic option for persistent arthritis of the knee, performed by intra-articular administration of ^{90}Yttrium (^{90}Y).[1,2] The mechanism of action is local radiation inducing necrosis of the synovial membrane, followed by fibrosis and sclerosis. After injection of ^{90}Y, the needle is flushed with glucocorticoids (GC) to prevent a chemically induced flare-up of arthritis and reflux of ^{90}Y, and to help to bridge the lag phase before the effect of RSO, which is assumed to last 3– 6 months.[1,3] GC could also reduce leakage of ^{90}Y into the blood by reducing within several hours synovitis and associated hypervascularity. It would seem plausible that a diffuse ^{90}Y distribution would predict a better outcome of RSO than focal distribution,[4] because of less surface contact between ^{90}Y and the inflamed synovial tissue in the latter situation. However, whether the distribution of ^{90}Y in the joint cavity after the injection is of importance for the clinical effect of RSO, has sparsely been investigated.

The aim of this study was to investigate the impact of the intra-articular ^{90}Y distribution on the clinical outcome of RSO and on its leakage from the joint.

Patients and methods

Patients

In a Dutch randomised clinical trial (RCT) the clinical effect of intra-articular ^{90}Y and GC versus that of GC was compared.[5]

Detailed data on the RCT have been described elsewhere.[5] Main outcome measure was a composite change index (CCI) (range 0–12), assessed 6 months after therapy being the lag phase of ^{90}Y.[6] The CCI included a functional disability score, Visual Analogue Scale of pain, joint tenderness, swelling and effusion of the knee, and patient's and physician's global assessment of the effect of therapy. Successful therapy was defined as CCI ≥6.

Crossover therapy was applied afterwards if there was treatment failure. The subgroups of RSO patients in whom distribution (n=78) and leakage (n=33) of ^{90}Y were assessed are the subject of this paper. RSO was applied using 185 MBq Yttrium-90 citrate (CIS bio international) and either 20 mg triamcinolone hexacetonide or 40 mg triamcinolone acetonide.

After injection, the knee was bent several times,[7] followed by splinting and 72 hours clinical bed rest.[8]

Methods

Assessments

a) distribution

Distribution was assessed in four centres, either immediately after RSO (one centre) or after 24 hours. The European Association of Nuclear Medicine (EANM) guidelines for

radiosynovectomy [9] lack a guideline on the interval of time between injection and assessment of distribution. ^{90}Y distribution was imaged with a Philips Vertex MCD dual-head gamma camera equipped with VXHR collimators, registering 'bremsstrahlung' during 10 min in a energy window (69 KeV ± 10%) and in a 256x256 matrix. Distribution was scored by the involved nuclear physician as follows: I) diffuse, II) predominantly diffuse, but also focal, III) predominantly focal, but also diffuse, or IV) focal (fig 1). There were no patients with extra-articular distribution. For some analyses, the four classes were compacted into two groups: 'mainly diffuse' (classes I&II) or 'mainly focal' distribution (classes III&IV).

b) leakage

Since assessment of leakage is not required according to the EANM guidelines,[9] leakage after 24 hours was measured in only three centres. Leakage was assessed with a Philips Vertex MCD dual-head gamma camera equipped with VXHR collimators at inguinal lymph nodes (n=15 RSOs), liver (n=33 RSOs), and spleen (n=18 RSOs). Counts in these regions were corrected for background radiation and expressed as percentage of counts corresponding with the whole injected dose.

Statistical analyses

The association between clinical effect and distribution pattern was explored by Spearman correlations, multiple linear regression analysis (dependent variable: CCI; independent variable: distribution classes I–IV by dummy variable coding) and logistic regression analysis (dependent variable: successful treatment ''yes'' or ''no'').

The association between leakage and distribution was explored by Spearman correlations. In the two groups ''mainly diffuse'' or ''mainly focal'' distribution, leakage was tested for statistically significant difference. Because in only 18 knees both leakage and distribution were assessed, no regression analyses were performed.

Tests were two-sided; p values <0.05 were considered to be statistically significant. Analyses were performed with Number Cruncher Statistical System 2000 and Statistical Package for Social Sciences, version 10.

Results

Baseline characteristics

In 69 patients 78 RSOs were performed; in nine patients both knees were treated. Patients suffered mainly from undifferentiated arthritis (42%) or RA (28%) (Table 1), and were 48±16

years old, range 19–76. Mean disease duration was 7±8 years, range 1–46, while mean duration of arthritis of the knee was 39±36 months, range 6–240. Most patients had pre-existing radiological damage of the treated knee (Steinbrocker radiological class I 28%, class II 71% and class III 1%). In 33%, ^{90}Y+GC was administered at crossover. At RSO, synovial fluid (SF) was successfully aspirated in 86%.

Distribution

^{90}Y distribution was ''mainly diffuse'' in 54% and ''mainly focal'' in 46%. Baseline variables were not different between these two groups. In RA, distribution was ''mainly diffuse'' in 64% versus 50% in non-RA (ie, all other diagnoses than RA) (p=0.3). The distribution pattern in patients in whom 24 hours after RSO distribution was assessed was not significantly different from the pattern in patients with an immediate assessment (p=0.8).

Distribution was more ''mainly diffuse'' if triamcinolone acetonide (n=13) was co-administered than if triamcinolone hexacetonide (n=65) was used (92% versus 46%, p=0.002), whereas there was a trend towards more ''mainly diffuse'' distribution if SF was aspirated than if not (57% versus 25%, p=0.1). In regression analyses, only the type of co-administered GC predicted distribution (r=-2.74, p=0.03).

Clinical effect was not significantly different between the two groups (response rate 40% for ''mainly diffuse'' distribution versus 56% for ''mainly focal'', p=0.3, CCI 5±3 versus 6±4, respectively, p=0.5), even if CCI was categorised (Table 1). CCI did not correlate with the four classes of distribution (r=0.06, p=0.6) and could neither be predicted by distribution. Neither clinical effect (p=0.8) nor intra-articular distribution (p=1.0) were significantly different in the crossover group.

Leakage

No ^{90}Y leakage to inguinal lymph nodes was found. Mean±SD leakage to the liver was 0.4±0.7%, range 0–2.5, and to the spleen 1.1±1.2%, range 0–5. Leakage to the liver (n=33) was significantly less if ''mainly diffuse'' distribution (n=18) than if ''mainly focal'' distribution (n=15) was present: 0.2±0.4% versus 0.9±0.8%, p<0.0001. Similar results were found for leakage to the spleen (n=18) (0.6±0.4% versus 1.6±1.3%, respectively, p=0.04). Leakage was not different in the crossover group. Distribution (class I–IV) was correlated with leakage to the liver (r=0.68, p<0.001) but not with leakage to the spleen (p=0.1), while leakage to the liver and to the spleen were correlated (r=0.86, p<0.0001). Clinical effect (CCI) was not correlated with leakage (counts) to the liver (p=0.9) or to the spleen (p=0.4).

*Table 1: the relation between intra-articular ^{90}Y distribution and the clinical effect of RSO, radiological class and leakagen (n = 78 knees)**

	Mainly diffuse Distribution	**Mainly focal distribution**	**P**
	n=42	n= 36	
Composite Change Index (CCI, 0-12)			
CCI, classified	**n (%)**	**n (%)**	0.6
	0 - 4	19 (45)	12 (33)
	4 - 8	15 (36)	16 (45)
	8 - 12	8 (19)	8 (22)
median (95% LCL-95% UCL)	5 (3-7)	7 (4-8)	0.5
Responders (CCI ≥ 6), n (%)	17 (40)	20 (56)	0.3
Radiological class	**n (%)**	**n (%)**	0.2
I	14 (35)	7 (20)	
II	25 (63)	28 (80)	
Leakage (% of given dose)†			
to the liver			
number of assessments	18	15	
mean (SD)	0.2 (0.4)	0.9 (0.8)	0.0004
leakage to liver, classified:	**n**	**n**	0.004
0	15	3	
0 - 1	2	7	
1 - 2	1	4	
2 -3	0	1	
to the spleen			
number of assessments	5	13	
mean (SD)	0.6 (0.4)	1.6 (1.3)	0.09
leakage to spleen, classified:	**n**	**n**	0.2
0	0	1	
0 - 1	5	5	
1 - 2	0	4	
2 - 3	0	2	
3 - 4	0	0	
4 - 5	0	1	

**78 knees: rheumatoid arthritis 22, undifferentiated arthritis 33, psoriaticarthritis 17, osteoarthritis 1, pigmented villonodular synovitis 1, synovialchondromatosis 1, ankylosing spondylitis 1, undifferentiated seronegative spondyloarthropathy 1, calcium pyrophosphate arthropathy 1. †Counts, expressed as percentage of total counts corresponding with the whole injected dose.*

Discussion

No association was found between intra-articular distribution of ^{90}Y and the clinical effect of RSO in nearly 80 knees, corresponding with data in the literature.[10] However, one study showed a trend towards earlier relapse of arthritis of the knee after poor intra-articular distribution,[4] but in patients with hydroxyapatite arthropathy undergoing RSO with Samarium-153.

In the present study, despite bending of the knee several times after RSO for better intra-articular dispersal of injected fluids,[7] distribution was still ''mainly diffuse'' in only 54%. ^{90}Y distribution appears to correspond to areas of increased synovial activity,[10 11] but it seems unrealistic to assume that patients with ''mainly focal'' distribution had focal synovial inflammation in the knee. However, since all patients had persistent arthritis, intra-articular septa or especially large synovial folds could have hampered the intra-articular distribution.

The distribution patterns in the different participating centres were not significantly different, indicating no influence of the injection technique on distribution.

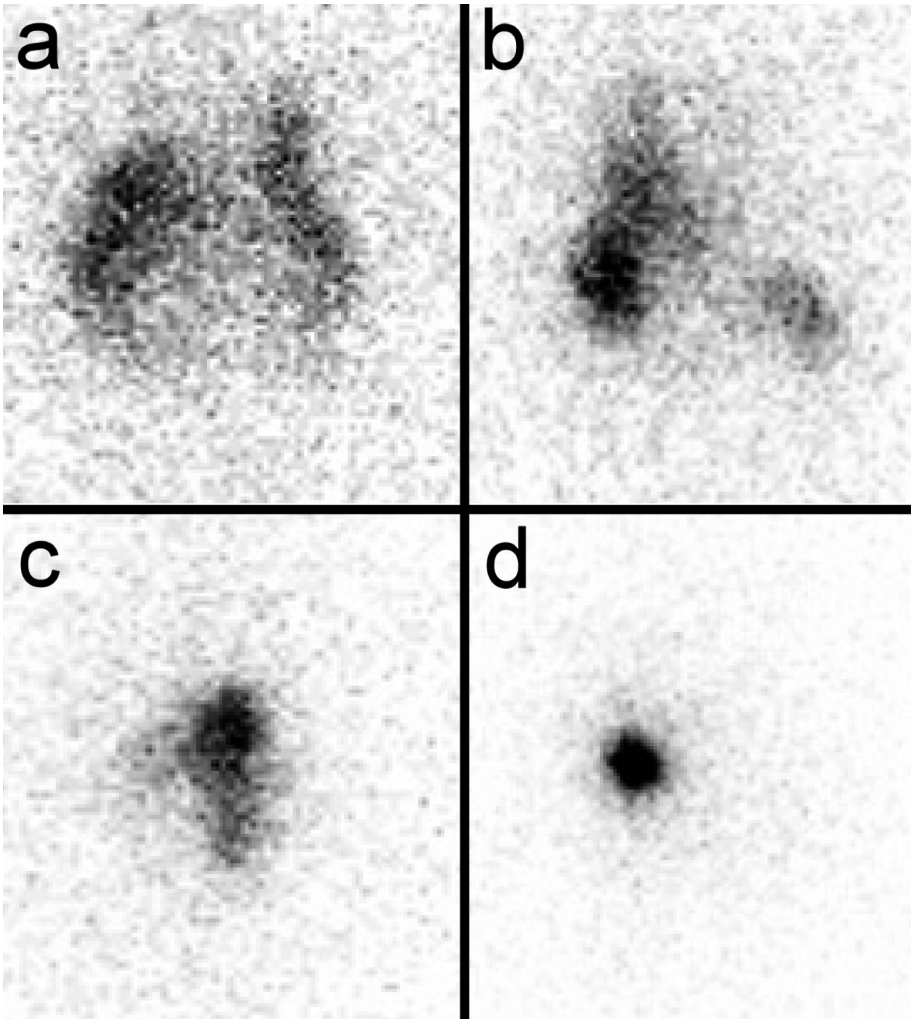
Unexpectedly, distribution was dependent on the type of GC used, perhaps due to the physical chemical properties of the different solvents or, less likely, of the compounds themselves.

As distribution did not predict the clinical effect and as there are no measures to take if the distribution scan indicates that the injection technique failed, standard assessment of distribution according to EANM guidelines[9] seems to serve no purpose.

Our leakage data are in accordance with the literature.[11–13] Leakage did not seem to hamper the clinical effect of RSO, although assessed in a small group. Despite the fact that an increased frequency of chromosomal aberrations in circulating lymphocytes after RSO has been reported,[8 90]Y does not seem to increase the risk of cancer.[14] So, in our opinion, the importance of leakage should not be overestimated. Whether RSO should be the treatment of first choice in the treatment of persistent arthritis of the knee, since in previous studies[5 15] superiority of RSO over GC alone was debatable and long-term results are limited, is discussed elsewhere.[5]

In conclusion, intra-articular ^{90}Y distribution does not influence the clinical effect of RSO of the knee. Although ^{90}Y leakage from the joint is less if ^{90}Y distributes diffusely in the joint cavity, leakage does not seem to hamper the clinical effect.

Figure 1: examples of scoring intra-articular distribution into the four classes I-IV A) diffuse (class I), B) predominantly diffuse, but also focal (class II), C) predominantly focal, but also diffuse (class III), and D) focal (class IV) distribution. The contour of the knee joint can be estimated from picture 1A.



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Chapter 6

Radiation synovectomy with ^{90}Yttrium, ^{186}Rhenium and ^{169}Erbium: a systematic literature review with meta-analyses

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Abstract

Objective: To perform a systemic review and meta-analysis on the effectiveness of radiosynoviorthesis (RSO).

Methods: A search of medical databases is conducted. Criteria for inclusion: articles in English, minimum follow-up of 6 months, definition of joint disease, reported outcome of at least 5 RSOs. The studies are scored for quality by the Oxford Centre of Evidenced-based Medicine levels of Evidence, from 1 to 4.

Results: Included are 21 studies (3 quality 1b, 5 2b and 13 4) analysing ^{169}Erbium/^{186}Rhenium-RSO used predominantly in small joints and 49 (1 quality 1b, 10 2b and 38 4) on ^{90}Yttrium-RSO used predominantly in knee joints. The reported success rates of ^{169}Erbium/^{186}Rhenium-RSO ranged from 69-100% at 6 months, and from 54-100% at ≥12 months; for ^{90}Yttrium they were 24-100% and 29-94%, respectively. Studies comparing the effect of RSO with that of glucocorticoid (GC) or saline injection alone were pooled. At 6 months the pooled odds ratio favouring RSO of the knee with Yttrium over control is 4 (confidential interval (CI) 95% 1.2-14), p=0.02, but at 12 months the ratio was 1.7 (CI95% 0.69-4), p=0.26. For RSO of small joints with Erbium/Rhenium compared to control, the pooled odds ratio at 6 months is 2 (CI95% 0.66-6) , p=0.22 and at 12 months 2 (CI95% 1.09-3.5), p=0.03.

Conclusion: Reported success rates of RSO are high, but differences in effect with GC injection are less evident, although there is marked heterogeneity in study design of the (small number of) comparative studies.

Introduction

Arthritis, e.g. rheumatoid arthritis (RA), is a common and chronic condition that is managed with both systemic and local drug treatment. Drugs comprise nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs), including biologicals and glucocorticoids (GCs), and intraarticular GC injections. In case synovitis persists, surgical, chemical or radiation synovectomy may be an option.

Radiation synovectomy or radiosynoviorthesis (RSO) is being used for decades. The injected small particles labelled with β-emitting isotopes are phagocytosed by macrophage-like synoviocytes and phagocytizing inflammatory cells, located in the subsynovial connective tissue (1). Radiation of the synovium results in necrosis of the synoviocytes and inflammatory cells; cell proliferation and synovitis are temporarily inhibited and progression of joint-damage is possibly delayed (2). The European Association of Nuclear Medicine (EANM) advises ^{90}Yttrium, ^{169}Erbium and ^{186}Rhenium colloids (3). These radiopharmaceuticals are at the moment the only commercially available isotopes for RSO in Europe.

The penetration depth of the β-rays should correspond to the thickness of the inflamed synovium. In soft tissue, β-rays from Yttrium-90 (^{90}Y; $t_{1/2}$ 2.7 days) have a mean/maximum penetration depth of 3.6/11 mm. For β-rays from Rhenium-186 (^{186}Re; $t_{1/2}$ 3.7 days), these numbers are 1.2/3.7 mm, and for β-rays from Erbium-169 (^{169}Er; $t_{1/2}$ 9.4 days), they are 0.3/1.0 mm. So, ^{90}Yttrium is used for RSO of the knee, ^{186}Rhenium for RSO of medium-sized joints and ^{169}Erbium for RSO of finger and toe joints.

Satisfactory control of synovitis has been reported in 40-80% of patients after one year, with a decline in symptom control over time (4). In a meta-analysis of 26 studies including 2190 treated joints, the efficacy of RSO ranged from 52-73%, depending on morphologic joint destruction (5). In contrast, two literature reviews did not find evidence to favour the effect of RSO with ^{90}Yttrium colloids over that of GC, osmic acid or surgical synovectomy (6,7). However, ^{90}Yttrium was superior to saline (7). Their conclusions were based on respectively only 2 and 10 studies and limited to RA patients and knee joints. However, RSO is not limited to the knee joint, and is also used for other inflammatory arthritides than RA and for osteoarthritis.

In this systematic literature review, the grade of recommendation or evidence for RSO is evaluated.

Materials and Methods

Two authors (FMvdZ and ROB) independently performed a formal computer-assisted search of the Medline, Embase, Cochrane Library and CINAHL databases (January 1971 to

February 2007). The following keywords, including synonyms, and medical subject headings were used: radiation synovectomy or radiosynoviorthesis, ^{169}Erbium, ^{186}Rhenium, ^{90}Yttrium. A manual search with cross-reference of eligible articles to identify additional relevant articles was also performed.

The same two authors assessed articles for possible inclusion in the review by checking titles and abstracts. Criteria for their inclusion in the analysis were: (1) articles published in the English language, (2) a minimum follow-up of 6 months, (3) definition of the joint disease, and (4) reported outcome of at least 5 RSO procedures.

Duplicate papers involving studies in the same patients were excluded. The final decision about inclusion was based on the full article. Disagreement was resolved in a consensus meeting.

The included articles were scored for quality by the Oxford Centre of Evidenced-based Medicine levels of Evidence for therapy studies (http://www.cebm.net/index.aspx?o=1025).

Level 1a = systematic review of randomised clinical trials (RCT).

Level 1b = individual RCT.

Level 1c = all or none (e.g. all patients died before the therapy became available, but now some survive on it).

Level 2a = systemic review of cohort studies.

Level 2b = individual cohort study or low quality RCT (e.g. , <80% follow-up).

Level 2c = ”outcomes” research; ecological studies.

Level 3a = systemic review of case-control studies.

Level 3b = individual case-control study.

Level 4 = case-series (and poor quality cohort and case-control studies).

Level 5 = expert opinion without explicit critical appraisal, or based on physiology, bench or ”first principles”.

The included studies with ^{169}Erbium and/or ^{186}Rhenium are listed in Table 1 and the included studies with ^{90}Yttrium are listed in Table 2. The level 1b and 2b studies are described in detail in this paper to give more insight in methods and effects. Furthermore, meta-analyses of level 1b and 2b studies, comparing the effect of RSO to that of saline or GC injection were performed, using the statistical software CMA v.2.

Results

Included studies

The Medline database produced most hits. ”Radiation synovectomy” yielded 248 hits; “radiosynoviorthesis” 73; “Erbium-169” 18; “Rhenium-186” 153 and “Yttrium-90” 669 hits.

Twenty-one studies analysing the effect of RSO with ^{169}Erbium and/or ^{186}Rhenium

have been included and are listed in Table 1 (8-28). The quality level was 1b in 3 (14%), 2b in 4 (19%) and 4 in 14 (67%). A RCT, in which there was a dropout rate of 47%, no statistical analysis and no information on blinding was scored as level 4 (17). A retrospective comparative study, in which it was unclear how joints were selected for RSO or for osmic acid and who scored the effect, also was scored as level 4 (19). All other studies were case series and scored as level 4. In total, the effect of RSO in 4379 joints has been studied. The success percentage of RSO ranged from 69 to 100 at 6 months and from 54 to 100 at 12 months.

Forty-nine studies analysing in a total of 3540 joints the effect of RSO with ^{90}Yttrium were included and are listed in Table 2 (9,11,15,18-21,26,37, 29-68). The quality level was 1b in 1 (2%), 2b in 10 (18%) and 4 in 38 (78%). A RCT, in which patients' characteristics were not mentioned nor the results were specified, was scored as level 4 (37). The study of the Arthritis and Rheumatism Council was scored as level 4 because it had been discontinued because of dwindling recruitment (43). All other studies were case series studies, level 4. The percentages of joints, which benefit from RSO with ^{90}Yttrium ranged from 24 to 100 at 6 months and from 29 to 100 at 12 months.

Level 1b and 2b studies with ^{169}Erbium and/or ^{186}Rhenium

Menkes compared the effect of ^{169}Erbium+prednisolone (121 joints) with that of saline+prednisolone (80 joints) in finger joints of 36 RA patients (10). The parameters synovial thickness, synovial effusion and range of movement were used for assessment of the effect. For ^{169}Erbium+prednisolone, the results at 6-12 months were excellent/good for 58% of joints, for 30% fair and for 12% poor versus 28% excellent/good, 31% fair and 31% poor for saline+prednisolone, $p<0.01$.

Ruotsi investigated 32 RA patients (12). The results of 83 finger joints treated with ^{169}Erbium were compared with those of 54 finger joints treated with injections of triamcinolone. The results at 6 months for ^{169}Erbium were excellent in 34% of joints, in 29% good, in 20% moderate and in 17% bad versus 52% excellent, 11% good, 30% moderate and 7% bad, respectively, for triamcinolone, $p=0.01$. At 12 months, the results were 39%, 21%, 31% and 9%, respectively, for ^{169}Erbium and 45%, 18%, 25% and 7% for triamcinolone, $p>0.05$. At 18 months, they were 39%, 20%, 37% and 4%, respectively, for ^{169}Erbium and 53%, 19%, 22% and 6%, respectively, for triamcinolone, $p>0.05$.

Boussina studied the effect of ^{169}Erbium versus that of injection with saline in 20 paired metacarpophalangeal (MCP) joints and 15 paired proximal interphalangeal (PIP) joints in 7 RA patients (13). The joints had been resistant to local injections with 20 mg of prednisolone-butylacetate. Excellent/good results were defined as disappearance of synovitis and pain, or decrease in synovitis and pain (≥75%). All other results were defined as fair no improvement. ^{169}Erbium yielded excellent/good results in 72% of joints and fair or no improvement in 28% at 6 months, versus excellent in 40% and fair or no improvement in 60% for saline, $p<0.01$. At

Table 1: studies analysing effect of radiosynoviorthesis with ^{169}Erbium and/or ^{186}Rhenium

First author Year[ref]	Isotope	Total joints	Shoulder Joints	Elbow joints	Wrist joints	Finger Joints1	Knee joints	Hip joints	Ankle joints	MTP2 joints
Menkes 1973[8]	^{169}Erbium ^{186}Rhenium	380	0	0	153	227	0	0	0	0
Delbarre 1974[9]	^{169}Erbium ^{186}Rhenium	134	18	26	50	20	0	5	15	0
Menkes 1977[10]	^{169}Erbium	121	0	0	0	121	0	0	0	0
Menkes 1979[11]	^{169}Erbium ^{186}Rhenium	1860	215	176	561	794	0	0	114	0
Ruotsi 1979[12]	^{169}Erbium	83	0	0	0	83	0	0	0	0
Boussina 1979[13]	^{169}Erbium	35	0	0	0	35	0	0	0	0
Gumpel 1979[14]	^{169}Erbium	82	0	0	18	64	0	0	0	0
Andjelkovic 1993[15]	^{169}Erbium ^{186}Rhenium	262	2	6	7	330	0	0	17	0
Fernandez-Pallazi 1996[16]	^{186}Rhenium	10	1	1	0	0	6	0	2	0
Göbel 1997[17]	^{186}Rhenium	41	?	?	?	0	0	?	?	0
Gratz 1999[18]	^{169}Erbium ^{186}Rhenium	30	8	3	4	7	0	1	7	0
Molho 1999[19]	^{169}Erbium ^{186}Rhenium	50	5	30	0	0	0	0	15	0
Jahangier 2001[20]	^{169}Erbium ^{186}Rhenium	98	5	26	28	11	0	13	15	0
Kampen 2001[21]	^{169}Erbium ^{186}Rhenium	388	8	22	71	214	0	0	26 + 22 Subtalar	23 + 2 tarsal
Tebib 2004[22]	^{186}Rhenium	65	11	10	38	0	0	0	6	0
van der Zant 2004[23]	^{186}Rhenium	54	0	0	0	0	0	0	54	0
Kahan 2004[24]	^{169}Erbium	39	0	0	0	39	0	0	0	0
Kampen 2005[25]	^{169}Erbium	53	0	0	0	53	0	0	0	0
Grmek 2005[26]	^{186}Rhenium	11	0	5	1	0	0	0	5	0
Rau 2005[27]	^{169}Erbium ^{186}Rhenium	546	57 + 1 AC[10]	32	87	272	0	12	39 + 21 subtalar	25 + 1 tarsal
van der Zant 2006[28]	^{169}Erbium ^{186}Rhenium	37	2	8	20	7	0	0	0	0

[1]Finger joints = Metacarpophalangeal joints, interphalangeal 1 joint, proximal interphalangeal joint, distal interphalangeal joint, [2]MTP = Metacarpophalangeal joint, [3]RA = Rheumatoid Arthritis, [4]? = No or not mentioned,

Disease	Failure to previous intra-articular GC	Co-administration of GC	Effect % ±6 months	Effect% ≥12 months	Quality of study	Compared to and P value
RA[3]	?[4]	No	70%	71%	4	NA5
RA	?	No	?	72%	4	NA
RA	?	Yes	?	88%	2b	Saline+prednisolone P<0.01
RA+ other[6]	?	No	78%	76%	4	NA
RA	?	No	83%	81%	2b	Triamcinolone P>0.05
RA	Yes	No	72%	79%	2b	Saline P<0.01
RA+PA[7]	Yes only 2 patients	No	?	54%	2b	Methylprednisolone P>0.05
RA	?	No	?	80%	4	NA
HH[8]	?	No	?	88%	4	NA
RA	?	Yes	100%	100%	4	RSO versus RSO+GC versus GC P=?
RA	?	Yes	100% ^{169}Er 90% ^{186}Re	?	4	NA
HH	?	No	88%	?	4	Osmic acid P<0.001
RA+ other	Yes	Yes	?	70%	4	NA
RA+ other	?	No	?	67%	4	NA
RA	?	No	88%	82%	1b	Cortivazol P=0.02
RA+ other	Yes	Yes	?	78%	4	NA
Ra	Yes	No	95%	?	1b	Saline P=0.002
OA[9]	Yes	No	?	68%	4	NA
HH	?	No	88%	82%	4	NA
RA+ other	?	No	?	60%	4	NA
RA+ other	Yes	Yes	69%	69%	1b	Triamcinolone P=0.004

[5]NA = Not applicable, [6]Other = Other inflammatory arthritis, osteoarthritis and pigmented villonodular synovitis, [7]PA = Psoriatic Arthritis, [8]HH = Haemophilic Hemarthrosis, [9]OA = Osteoarthritis, [10]AC = Acromioclavicular joint.

Table 2: studies analysing effect of radiosynoviorthesis with ^{90}Yttrium

First author Year[ref]	Isotope	Total joints	Knee joints	Other joints	Disease	Failure to previous intraarticular GC
Bridgman 1971[29]	^{90}Yttrium	22	22	0	RA[1] + OA[2] + PA[3]	Yes
Delbarre 1974[9]	^{90}Yttrium	106	106	0	RA	?
Müller 1975[30]	^{90}Yttrium	45	37	4 hip + 4 ?	RA+ Other[6]	Yes (75%)
Jalava 1975[31]	^{90}Yttrium	62	62	0	RA	?
Oka 1975[32]	^{90}Yttrium	48	48	0	RA	?
Gumpel 1975[33]	^{90}Yttrium	10	10	0	RA+ other	Yes
Doyle 1977[34]	^{90}Yttrium	15	15	0	RA+ other	Yes
Szanto 1977[35]	^{90}Yttrium	33	33	0	RA+ other	Yes
Nissilä 1978[36]	^{90}Yttrium	23	23	0	RA	?
Yates 1979[37]	^{90}Yttrium	33	33	0	RA	?
Menkes 1979[11]	^{90}Yttrium	547	547	0	RA+ other	?
Winfield 197938	^{90}Yttrium	30	30	0	RA+ other	Yes
Doherty 1981[39]	^{90}Yttrium	15	15	0	Pyrophosphate arthropathy	?
Sheppeard 1981[40]	^{90}Yttrium	84	84	0	RA	Yes
Stojanovic 1982[41]	^{90}Yttrium+ ^{198}Au	26	26	0	RA	?
Kyle 1983[42]	^{90}Yttrium	28	28	0	RA	Yes
ARC 1984[43]	^{90}Yttrium	20	20	0	RA	Partly
Spooren 1985[44]	^{90}Yttrium	48	48	0	RA + OA	?
Boerbooms 1985[45]	^{90}Yttrium	23	23	0	RA	Yes
Sheldon 1986[46]	^{90}Yttrium	27	27	0	RA+ other	?
Franssen 1989[47]	^{90}Yttrium	8	8	0	PVS[7]	?
Erken 1991[48]	^{90}Yttrium	58	27	2 shoulder 14 elbow 14 ankle	HH[8]	?
Grant 1992[49]	^{90}Yttrium	14	14	0	RA	Yes > 6 months
Will 1992[50]	^{90}Yttrium	103	89	6 shoulder 1 elbow 7 hip	RA + OA + other	Partly
Van Kasteren 1993[51]	^{90}Yttrium	16	10	3 elbow 1 wrist 2 ankle	HH	?

	Co-admistration of GC	Effect % at ±6 months	Effect % at ≥12 months	Quality of study	Compared to and P value
	No	68%	?[4]	2b	Saline P=0.01
	No	?	89%	4	NA[5]
	Yes	43%	?	4	NA
	No	70%	?	4	NA
	No	77%	73%	4	NA
	No	?	70%	2b	Surgical synovectomy P>0.05
	No	?	53%	4	NA
	No	77%	59%	2b	prednisolone P<0.01
	No	?	52%	2b	osmic acid and surgical synovectomy P>0.05
	No	?	?	4	Non radioactive Yttrium P=?
	No	74%	85%	4	NA
	No	63%	?	4	NA
	Yes	93%	?	2b	Saline+triamcinolone P<0.01
	No	62%	58%	2b	Osmic acid P>0.05
	Yes	?	57%	2b	Prednisolone P>0.05
	Yes	54%	?	4	NA
	No	?	?	4	Triamcinolone P=?
	No	?	60%	4	NA
	No	43%	35%	4	NA
	No	24%	?	4	NA
	No	38%	50%	4	NA
	No	?	81%	4	NA
	No	64%	?	2b	Triamcinolone P>0.05
	Yes	?	56%	4	NA
	No	?	94%	4	NA

Table 2: studies analysing effect of radiosynoviorthesis with ^{90}Yttrium

First author Year[ref]	Isotope	Total joints	Knee joints	Other joints	Disease	Failure to previous intraarticular GC
Andjelkovic 1993[15]	^{90}Yttrium	155	155	0	RA	?
Stucki 1993[52]	^{90}Yttrium	164	103	24 shoulder 11 elbow 3 hip 23 ankle	RA+ other	Yes
Dawson 1994[53]	^{90}Yttrium	34	9	3 shoulder 12 elbow 10 ankle	HH	?
Edmonds 1994[54]	^{90}Yttrium	29	29	0	RA + OA	?
Hilliquin 1996[55]	^{90}Yttrium	76	76	0	OA	?
Jahangier 1997[56]	^{90}Yttrium	83	83	0	RA+ other	Yes
Asavatanabodee 1997[57]	^{90}Yttrium	133	133	0	RA+ other	Yes
Taylor 1997[58]	^{90}Yttrium	121	121	0	RA+ other	?
Alonso-Ruiz 1998[59]	^{90}Yttrium	10	10	0	RA	Yes
Gratz 1999[18]	^{90}Yttrium	6	6	0	RA	?
Molho 1999[19]	^{90}Yttrium	35	35	0	HH	?
Kat 2000[60]	^{90}Yttrium	8	8	0	PVS	?
Jahangier 2001[20]	^{90}Yttrium	40	40	0	RA+ other	Yes
Heim 2001[61]	^{90}Yttrium	115	75	27 elbow 13 ankle	HH	?
Rodriguez-Merchan 2001[62]	^{90}Yttrium	66	45	12 elbow 9 ankle	HH	?
Kampen 2001[21]	^{90}Yttrium	87	87	0	RA+ other	?
Shabat 2002[63]	^{90}Yttrium	10	7	1 hip 3 ankle	PVS	?
Gencoglu 2002[64]	^{90}Yttrium	24	24	0	RA	?
Jacob 2003[65]	^{90}Yttrium	38	38	0	RA+ other	Yes
Kraft 2005[66]	^{90}Yttrium	408	408	0	RA+ other	?
Grmek 2005[26]	^{90}Yttrium	6	6	0	HH	?
Rau 2005[27]	^{90}Yttrium	257	257	0	RA+ other	?
Jahangier 2005[67]	^{90}Yttrium	86	86	0	RA+ other	Yes
Kavakli 2006[68]	^{90}Yttrium	105	56	2 shoulder 24 elbow 23 ankle	HH	?

[1]RA = Rheumatoid Arthritis, [2]OA = Osteoarthritis, [3]PA = Psoriatic Arthritis, [4]? = No or not mentioned

	Co-admistration of GC	Effect % at ±6 months	Effect % at ≥12 months	Quality of study	Compared to and P value
	No	?	78%	4	NA
	Yes	?	60%	4	NA
	Yes	88%	88%	4	NA
	No	53%	30%	2b	[165]Dysprosium P>0.05
	No	44%	?	4	NA
	Yes in majority	75%	29%	4	NA
	No	82%	75%	4	NA
	Yes	?	56%	4	NA
	Yes	90%	?	4	NA
	Yes	100%	?	4	NA
	No	88%	?	4	Osmic acid P<0.001
	No	?	100%	4	NA
	Yes	?	68%	4	NA
	Yes	?	80%	4	NA
	No	?	77%	4	NA
	No	?	64%	4	NA
	No	?	90%	4	NA
	No	58%	54%	4	NA
	No	68%	68%	4	NA
	No	92%	72%	4	NA
	No	67%	33%	4	NA
	No	?	64%	4	NA
	Yes	48%	49%	1b	Placebo+GC P>0.05
	No	?	83%	4	NA

[5]NA = Not applicable, [6]Other = Other inflammatory arthritis, PA and/or OA, [7]PVS = Pigmented Villonodular Synovitis, [8]HH = Haemophilic Hemarthrosis.

12 months, the results were classed as excellent/good in 79% and fair or no improvement in 21% for ^{169}Erbium and excellent/good in 50% and fair or no improvement in 50% for saline, $p<0.05$.

Gumpel studied 21 Ra patients and 3 Psoriatic Arthrites (PA) patients (14). The clinical effect in 18 wrists, 55 MCPs, 9 PIPs treated with ^{169}Erbium was compared with that of 12 wrists, 44 MCPs, 9 PIPs treated with methylprednisolone injection. The results at 12 months for ^{169}Erbium were remission in 1.2% of treated joints, marked reduction in 23%, minimal improvement in 29% and unchanged in 46%, versus resolution in 1.6%, marked reduction in 22%, minimal improvement in 27% and unchanged in 50% for methylprednisolone.

Tebib compared the effect of ^{186}Rhenium (65 joints) with that of 3.75 mg cortivazol, a phenylpyrazolo glucocorticoid, (64 joints) in 81 RA patients (22). Shoulder, elbow, wrist and ankle joints were studied. A 4-point scale (from 0=no signs to 4=most severe signs) was used. There were no significant differences at 6 nor at 12 months; in both treatment groups, success rates were 70% for pain, 53% for swelling and 42% for mobility. At 24 months the percentages of joints with decrease of pain were 90% for ^{186}Rhenium versus 70% for GC, $p=0.02$; 80% versus 40% showed a decrease of joint swelling, respectively, $p=0.01$; 95% versus 80% showed a decrease of pain *or* swelling, respectively, $p=0.03$; 75% versus 40% showed a decrease of pain *and* swelling, $p=0.02$.

Kahan investigated 82 finger joints in 42 RA patients (24). ^{169}Erbium was administered in 39 joints and saline in 43 joints. All joints had failed to a previous GC injection. At 6 months, 95% of the joints treated with ^{169}Erbium showed decreased of pain or of swelling versus 79% of those treated with saline; $p=0.04$. At 6 months, 79% of the joints treated with ^{169}Erbium showed decrease in both pain and swelling, versus 47% of those treated with saline; $p=0.002$.

Van der Zant studied 49 RA joints, 9 PA joints and 10 joints with arthritis of unknown origin of 44 patients (28). Twenty radiocarpal joints, 8 elbows, 2 glenohumeral joints and 7 finger joints were injected with ^{169}Erbium or ^{186}Rhenium+triamcinolone and 20 radiocarpal joints, 5 elbows, 1 glenohumeral joint and 5 finger joints with placebo+triamcinolone. All treated joints had failed to a previous intraarticular GC injection, defined as no relief of symptoms or relapse within 3 months. Success rates were determined by a change composite index (CCI), composed of scores for functional disability score, 10 cm visual analogue scale (VAS) of pain, joint tenderness, joint swelling, patient's global assessment and physician's assessment. The CCI could range from 0 (failure) to 12 (maximal effect). CCI ≥ 6 was considered as a success. The success rates were 69% (for RA 74% versus 56% for non-RA) of joints for ^{169}Erbium or ^{186}Rhenium+triamcinolone versus 29% (for RA 18% versus 56% for non-RA) for placebo+triamcinolone at 6 months ($p=0.001$) and 69% (for RA 81% versus 33% for non-RA) versus 32% (for RA 22% versus 57% for non-RA), respectively, at 12 months ($p=0.004$).

Level 1b and 2b studies with ^{90}Yttrium

Bridgman studied 19 patients with RA, 2 with osteoarthritis OA and 1 with PA (29). The effect of 111 MBq ^{90}Yttrium (the advised dose is 185 MBq) in 22 knees was compared with that of intraarticular injections with saline in 20 knees. The treated knees had failed to a previous intraarticular GC injection. The outcome parameters were pain, joint range of motion, knee circumference and effusion. Significant improvement was found for joint effusion in 68% for ^{90}Yttrium versus 35% of patients treated with saline (p=0.01) and joint range in 45% for ^{90}Yttrium versus 0% of patients treated with saline (p=0.001). There were no significant differences for pain and knee circumference.

Gumpel compared in 17 patients, 15 with RA, 2 with PA, the effect of 10 RSOs with that of 11 surgical synovectomies in joints with arthritis which failed to a previous intraarticular GC injection (33). Using a scoring system of 0-4 (0=no improvement to 4=maximal improvement) to assess symptomatic improvement, the mean score for surgical synovectomy was slightly higher: 3.1 versus 2.7. The composite score (comprising knee circumference, range of movement and assessment of stability of the knee) was 3.7 for surgical synovectomy versus 3.5 for RSO, p>0.05. After a mean follow-up of 2 years, synovitis progressed in 3 joints in the RSO group versus 2 in the surgical synovectomy group; p>0.05.

Szanto studied in total 33 patients, 18 with RA, 5 with rheumatoid factor-negative chronic polyarthritis, 6 with PA and 4 with spondylitis, of whom 3 supposedly also had RA (35). In 25 patients with bilateral synovitis of the knee, the effect of treatment with ^{90}Yttrium in one knee was compared with that of repeated injections with methylprednisolone in the other knee of the same patient. Furthermore, 8 patients with unilateral synovitis were treated with ^{90}Yttrium. The included joints had been resistant to previous intraarticular GC injections. Percentages for excellent and good result of RSO were significantly higher from 3 months on (77% versus 10% of joints, p<0.001) to 42 months (40% versus 26%, p<0.01).

Nissilä compared the effects of chemical, radiation and surgical synovectomy of knee joints of patients with RA (36). Twenty-two patients were allocated to osmic acid, 23 to ^{90}Yttrium and 21 to surgical synovectomy. There was no significant difference in pain relief at 12 months. Fourteen patients of the ^{90}Yttrium group needed additional GC injections versus 7 in the osmic acid group and 11 in the surgical synovectomy group. The differences between the three therapies were not significant.

Doherty studied 15 patients with bilateral, symmetrical, chronic pyrophosphate arthropathy (39). One knee of each patient was allocated to ^{90}Yttrium and 20 mg triamcinolone, and, as control, the other knee was treated with saline and 20 mg triamcinolone. At 6 months, all outcome parameters were significantly more favourable for ^{90}Yttrium and GC with regard to pain, p<0.01, stiffness, p<0.01, joint-line tenderness, p<0.01, effusion, p<0.01, range of movement, p<0.01, and joint circumference, p<0.05.

Sheppeard compared the effect of ^{90}Yttrium (84 knees of 59 RA patients) with that of

osmic acid (91 knees of 67 RA patients) (40). The knees had failed to a previous GC injection. Response of RSO was defined as good pain relief, no joint tenderness/warmth, decreased synovial thickening/effusion and an increased range of movement. The response rates at 6 months, 1 year, 2 years and 3 years for ^{90}Yttrium were 62%, 58%, 48% and 40% of joints, respectively, versus 71%, 69%, 62% and 57%, respectively, for osmic acid. Thus, osmic acid appeared to be more effective, but the difference only reached statistical significance at 3 years ($p<0.05$).

Stojanovic studied 26 RA patients with bilateral synovitis of the knee (41). The effect of ^{198}Au or ^{90}Yttrium+GC (40 mg methylprednisolone) in one knee was compared that of saline+GC in the contralateral knee. The outcome parameters were pain, knee circumference, range of motion. After a mean follow-up of 42 months, the effect of RSO was good in 30% of joints; 27% of joints was improved and 43% was not improved, versus 19%, 38% and 43%, respectively, for methylprednisolone ($p>0.05$).

Grant studied 30 knee joints of 21 RA patients (49). In 9 patients with bilateral synovitis, one knee was allocated to ^{90}Yttrium and the other knee to GC. In addition, of 12 patients with unilateral synovitis of the knee, 7 were allocated to GC and 5 to ^{90}Yttrium. The effect of ^{90}Yttrium (296 MBq) was compared with that of 20 mg triamcinolone hexacetonide. At 6 months, triamcinolone had improved the range of motion more; $p<0.05$. The other outcome measures (pain at rest, pain walking, joint tenderness, knee effusion, and global change) showed no significant differences. After 6 years, 75% of joints initially treated with triamcinolone needed other treatment (reinjection with steroid and/or ^{90}Yttrium, surgical synovectomy or total knee arthroplasty), versus 66% of patients in the RSO group; $p>0.05$.

Edmonds compared the effect of intraarticular Yttrium-90 silicate with that of Dysprosium-165 hydroxide macro-aggregate (54). Seventy knees from 51 RA and 15 OA patients were randomly allocated to ^{90}Yttrium or ^{165}Dysprosium. At 24 weeks, more than 50% improvement of pain in walking, pain at rest and stiffness after rest was present in 47%, 53% and 30% of joints for ^{90}Yttrium, respectively, versus 44%, 37% and 46%, respectively, for ^{165}Dysprosium. At 52 weeks, the numbers were 15%, 9% and 30%, respectively, for ^{90}Yttrium versus 45%, 48% and 35%, respectively, for ^{165}Dysprosium. The differences were statistically not significant.

Jahangier studied clinical effect in 113 knees treated either with ^{90}Yttrium+GC or placebo+GC (67). The GC was in 80% of treatments 20 mg triamcinolone hexacetonide and in 20% of treatments 40 mg triamcinolone acetonide. Patients with arthritis (undifferentiated arthritis in 39%, RA in 32% and other diseases in 29%) despite at least 2 intraarticular GC injections that persisted for at least 4 weeks after the last injection were included. Furthermore, 18% had failed to previous radiation, surgical or chemical synovectomy. Success rates were assessed with the CCI described above. At 6 months, patients with persistent arthritis underwent crossover (45% of joints which initially were treated with ^{90}Yttrium+GC, and

51% of joints which initially were treated with placebo+GC). Success rates were 48% in both groups at 6 months. At 18 months, success rates dropped to 44% in the ^{90}Yttrium+GC group and 41% in the placebo+GC group; p>0.05. The success rates of ^{90}Yttrium+GC did not significantly differ between RA and non-RA patients: 44% at 6 months, 52% at 12 months and 48% at 18 months for RA versus 49%, 47% and 42%, respectively for non-RA.

Meta-analyses

Studies comparing the effect of RSO with that of GC or saline injection alone were pooled. At 6 months the pooled odds ratio favouring RSO of the knee with Yttrium over control is 4 (confidential interval (CI) 95% 1.2-14), p=0.02, but at 12 months the ratio is 1.7 (CI95% 0.69-4), p=0.26. For RSO of small joints with Erbium/Rhenium compared to control, the pooled odds ratio at 6 months is 2 (CI95% 0.66-6) , p=0.22 and at 12 months 2 (CI95% 1.09-3.5), p=0.03 Figures 1 and 2 show the forrest plots of these meta-analyses for respectively 6 and 12 months. These figures show the marked heterogeneity, also evident from statistically significant Q values as tests for heterogeneity, between studies, which could challenge the validity of the pooling. The number of studies however is too small to look for sources of heterogeneity and to pool for more homogeneous subgroups or to perform meta-regression. Analyses into possible publication bias (also hampered by the small number of studies) showed no significant Begg and Mazumdar rank correlation between the standardised effect sizes and variances of these effects; for the 2 significant pooled odds ratios found, adjusted values of the point estimates with Duval and Tweedie's trim and fill still were statistically significant and classic fail-safe N (number of missings studies to yield a non-significant p-value) was >10.

Discussion

The effect of RSO with ^{169}Erbium-, ^{186}Rhenium- and ^{90}Yttrium-colloids has been studied for decades. However, differences in study design, e.g. comparison of isotope with or without GC versus GC or placebo, respectively, differences in the used GC and different inclusion criteria, e.g. failure or not to previous intraarticular GC injection all hamper a clear comparison. Furthermore, there is no validated method measuring the clinical effect of RSO. Most investigators used clinical joint parameters like pain at rest, pain in lower extremity joints during walking, joint swelling, joint tenderness, effusion, etc. Others also have used the patient's and/or physician's global assessment of the effect of therapy (20,21,23,28,29).

Apart from clinical parameters, imaging modalities, arthroscopy and histology have been applied to assess the effect of RSO. The effect of RSO has been evaluated with ultrasonography, MRI, different nuclear medicine imaging techniques and thermographic

Figure 1: random effects model of isotope±GC versus saline or GC at 6 months.

6 months data

group by joint type	Study first author, reference	Comparison	Effect/Total		
			RSO	Control	
knee	Bridgman 29	Yttrium vs saline, 6 mo	15/22	9/20	
knee	Szanto 35	Yttrium vs GC, 6 mo	18/23	2/23	
knee	Doherty 39	Yttrium+GC vs GC, 6 mo	14/15	4/15	
knee	Grant 49	Yttrium vs GC, 6 mo	7/11	8/14	
knee	Jahangier 67	Yttrium+GC vs GC, 6 mo	41/86	39/81	
knee pooled					
small joint	Ruotsi 12	Erbium vs GC, 6 mo	69/83	50/54	
small joint	Bousina 13	Erbium vs saline, 6 mo	25/35	14/35	
small joint	Tebib 22	Rhenium vs GC, 6 mo	46/85	45/84	
small joint	Kahan 24	Erbium vs saline, 6 mo	37/39	34/43	
small joint	Zant 28	Erbium/Rhenium+GC vs GC, 6 mo	25/36	9/31	
small joint pooled					

CI = confidential interval, vs = versus, GC = glucocorticoid

	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
	2,6	0,74	9	0,13	
	38	6,53	219	0,00	
	39	3,75	395	0,00	
	1,3	0,26	7	0,74	
	1	0,53	1,8	0,95	
	4	1,24	14	0,02	
	0,4	0,12	1,3	0,12	
	4	1,38	10	0,01	
	1	0,56	1,9	0,94	
	5	0,99	24	0,05	
	6	1,94	16	0,00	
	2	0,66	6	0,22	

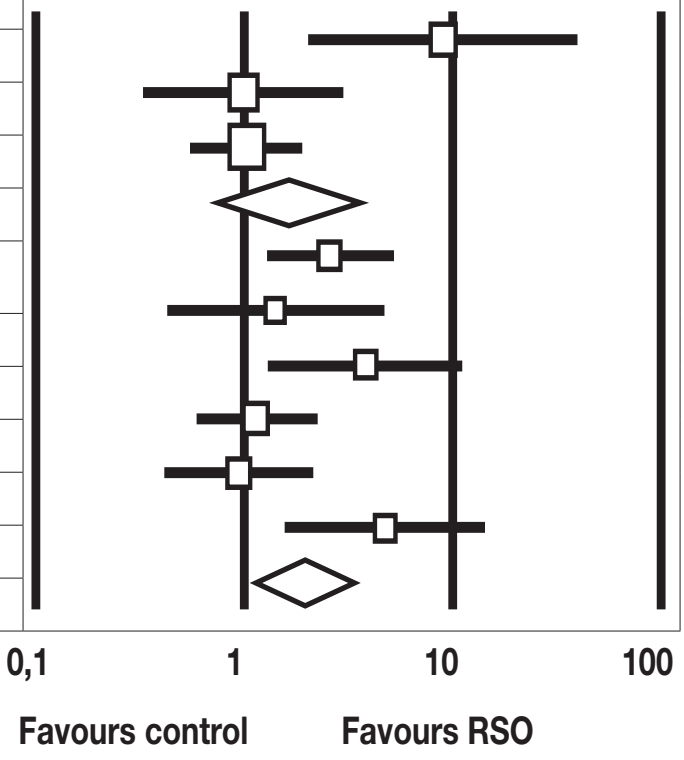
Figure 2: Random effects model of isotope±GC versus saline or GC at 12 months.

12 months data

Group by joint type	Study first author, reference	Comparison	Effect/Total		
			RSO	Control	
knee	Szanto 35	Yttrium vs GC, 12 mo	13/22	3/22	
knee	Stojanovic 41	Yttrium+GC vs GC, 12 mo	15/26	15/26	
knee	Jahangier 67	Yttrium+GC vs GC, 12 mo	42/86	39/81	
knee pooled					
small joint	Menkes 10	Erbium/Rhenium+GC vs GC, 12 mo	103/121	55/80	
small joint	Ruotsi 12	Erbium vs GC, 12 mo	64/70	45/51	
small joint	Bousina 13	Erbium vs saline, 12 mo	27/34	17/34	
small joint	Gumpel 14	Erbium vs GC, 12 mo	44/82	32/64	
small joint	Tebib 22	Rhenium vs GC, 12 mo	59/75	51/64	
small joint	Zant 28	Erbium/Rhenium+GC vs GC	25/33	11/28	
small joint pooled					

CI = confidential interval, vs = versus, GC = glucocorticoid

	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
	9	2,07	40	0,00	
	1	0,33	3	1,00	
	1	0,56	1,9	0,93	
	1,7	0,69	4	0,26	
	2,6	1,31	5	0,01	
	1,4	0,43	5	0,56	
	4	1,32	11	0,01	
	1,2	0,60	2,2	0,66	
	0,9	0,41	2,1	0,88	
	5	1,61	15	0,01	
	2	1,09	3,5	0,03	



imaging (18,21,31,42,59,66). Yates et al. found marked specific arthroscopic and histological changes accompanied with clinical improvement (37). Jahangier found that the number of macrophages in the synovial sublining was significantly higher in RSO responders than in non-responders ($p = 0.002$) (69). The effect of RSO in Haemophilic Hemarthrosis (HH) is, next to clinical and radiological parameters, assessed with the frequency of intraarticular bleeding and the need for clotting agents (26,62,68). Thus, the effect of RSO has been demonstrated by clinical parameters, morphological and histological findings. The results of RSO seem to be best in RA, followed by other inflammatory arthitides and HH. RSO is least effective in OA (27,50,58), although effect percentages up to 68 have been found (25).

Meta-analyses of level 1b and 2b studies show pooled odds ratio favouring RSO of the knee with Yttrium over control (saline or GC) 4 (CI 95% 1.2-14) at 6 months, $p=0.02$. However, at 12 months the ratio is 1.7 (CI95% 0.69-4), $p=0.26$. For RSO of small joints with Erbium/Rhenium compared to control, the pooled odds ratio at 6 months is 2 (CI95% 0.66-6) , $p=0.22$ and at 12 months 2 (CI95% 1.09-3.5), $p=0.03$. Yttrium and Erbium are more effective than saline. The efficacy of Erbium or Rhenium is equal to GC. In 2 studies Erbium or Rhenium+GC is superior to GC. Yttrium is more effective than GC in 2 studies and equal effective in 1 study. Two studies show comparable success rates between Yttrium+GC and GC. Yttrium is neither superior nor inferior to osmic acid or surgical synovectomy.

Which patients benefits most of RSO or how to select the best candidate for RSO is hardly studied. A low radiological damage score, no joint instability and/or axial deviation and a body mass index BMI below the 85th percentile are characteristics for favourable outcome of RSO of the knee (70). In our opinion the best candidates for RSO are patients with persistent synovitis after 1 intraarticular GC injection or recurrence of synovitis after 1 intraarticular GC injection within 3 months of one or a few joints in whom the disease in other joints is fairly well controlled. The duration of the persistent synovitis should not be too long, and there should be minimal radiological damage.

One comparative study in English was excluded because it was a duplicate study (71). There are a few trials written in other languages (72,73). Delbarre observed a statistically significant superiority of ^{90}Yttrium over non-radioactive ^{89}Yttrium. Urbanová compared the effect of ^{90}Yttrium with that of ^{90}Yttrium and GC or GC alone. Their study recommended ^{90}Yttrium without GC. Apart from RCTs, other case series on the effect of RSO have been published in French, German and Spanish. In our opinion, the results of these studies do not alter the conclusions of this systemic review.

Conclusion

Reported success rates of RSO are high, but differences in effect with GC injection are less evident, although there is marked heterogeneity in study design of the (small number of) comparative studies.

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Chapter 7

Thesis summary, general discussion and conclusions

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Summary

Inflammatory arthritis is common (1-4). It can be controlled with both systemic (nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids (GCs) and local drug treatment (intra-articular GC injections). In addition to drug treatment, physiotherapy, occupational therapy, adaptations and devices such as braces next to life style changes may be recommended as well. In a late phase, joint surgery may be indicated. If chronic synovitis persists in one or a few joints after non-invasive treatment, surgical, chemical, or radiation synovectomy, which is the removal (surgical synovectomy) or destruction (chemical and radiation synovectomy) of inflamed joint tissue, may be an option.

In **chapter 1**, the introduction, we describe radiation synovectomy, also called radiosynoviorthesis (RSO). RSO is being practiced for decades, with the first RSO clinical results published in 1952 (5). In RSO, small particles labeled with β-emitting isotopes are injected intra-articularly; these particles are subsequently engulfed by macrophage-like synoviocytes and phagocytizing inflammatory cells in the subsynovial connective tissue (6). This results in synoviocyte and inflammatory cell necrosis and inhibited cell proliferation. Synovitis and, possibly, progression of joint damage can be halted temporarily by RSO (7). Currently, ^{90}Yttrium, ^{169}Erbium, and ^{186}Rhenium colloids are the only commercially available isotopes recommended for use in RSO in Europe by the European Association of Nuclear Medicine (EANM) (8).

The reported results of RSO often regard RSO without co-administration of GC and/or without the inclusion criterion of insufficient effect of a previous intra-articular GC injection. Therefore, these results are not mirroring current clinical practice, in which RSO is performed with co-administration of GC and only if a previous intra-articular GC injection at the outpatient clinic was not effective enough. Furthermore, the reported results of RSO are predominantly based on the results of RSO of knee and finger joints and between studies the used outcome measures differ quite a lot . Up till now the effect of leakage and inhomogeneous distribution on the effect of RSO have not been studied.

In this thesis the results of RSO with ^{90}Yttrium, ^{169}Erbium, and ^{186}Rhenium colloids as advised by the EANM are studied. Leakage and distribution of the radionuclide are analyzed and their effect on the effectiveness of RSO and a systematic literature review is performed to evaluate the evidence for RSO.

In **chapter 2** we describe retrospectively the effect, effect duration, and safety of RSO of the tibio-talar (ankle) joint. Leakage from the joint and the radiation dose to target and non-target organs is estimated.

Fifty-four consecutive tibio-talar RSO treatments in 40 patients (28 women, 12 men; mean age 58 years, range 33-76) were scored as follows: 1, no effect; 2, moderate effect; or 3, good

effect. No effect was found in 12 of 54 (22%) of the treated joints, a moderate effect was found in 12 (22%) joints, with a mean effect duration of 34 months (range 12–49), and a good effect was found in 30 (56%) joints, with a mean effect duration of 41 months (range 21–75). No adverse effects were recorded.

Leakage was expressed as percentage of the injected dose. Mean leakage ± standard deviation (SD) for all procedures was 2.4 ± 3.0% for leakage to the lymph nodes and 0.8 ± 1.7% for leakage to the liver. No significant differences in leakage were observed in the 3 groups scored for RSO effectiveness.

The radiation dose to the synovium ranged from 2.76 Gray (Gy) to 3.05 Gy, depending on the amount of leakage. The maximal dose to a single lymph node was estimated to be ~35 Gy, the leaked radiation is absorbed by lymph nodes with a small volume (mm3), resulting in a high single lymph node dose. Adverse effects of the relative high single lymph node dose have not been described in literature or experienced in clinical practice. The maximal dose to the liver was ~0.0075 Gy.

In conclusion, RSO of the ankle is effective in 78%, although all patients eventually experienced recurrence of arthritis. Leakage of the radionuclides is generally quite low and RSO of the tibo-talar joint is save.

In **chapter 3** we describe a double blinded study comparing the clinical efficacy of RSO using intra-articular injections of radionuclide plus GC (group A) to that of injections of placebo plus GC (group B) for the treatment of persistent synovitis in joints of the upper extremity.

Forty-four patients were randomly allocated to group A or group B. The radionuclide dose and type and the GC (triamcinolone acetonide) dose for each joint type were as described in Table 2 in the introduction of the thesis. The duration of the study was 12 months. To evaluate clinical efficacy, a change composite index (CCI) was calculated using changes in the scores of six clinical variables over time. The six variables were as follows:

1. A *functional disability* score of the treated joint, assessed by the primary investigator based on the complaints of the patients: 0 (no complaints) – 3 (severe disability of the affected joint).
2. *A visual analogue scale (VAS) score of pain* for the treated joint, assessed by the patient: 0 mm (no pain) – 100 mm (maximal pain).
3. *A joint tenderness score* upon palpation of the affected joint: 0 (no tenderness) – 3 (wincing and withdrawing when pressure is applied).
4. *A joint swelling* score assessed by primary investigator: 0 (no swelling) – 3 (major swelling).
5. *Patient's global assessment score* of the effect of therapy: 0 (no improvement or worsening symptoms) – 3 (great improvement).

6. *Physician's global assessment score* of the effect of therapy: 0 (no improvement or worsening symptoms) – 3 (great improvement).

A change in time for the better of 1 added 1 point to the CCI, a change of 2 or 3 added 2 points to the CCI, respectively. No change or changes for the worse added 0 points to the CCI. The score could range from 0 (failure) to 12 (maximal positive effect of RSO). RSO was considered successful if the CCI ≥6, whereas a CCI <6 indicated treatment failure. Sixty-eight intra-articular injections in 44 patients (23 female and 21 male) were analysed; of the 68 injections, 37 were radionuclide plus GC and 31 were placebo plus GC. The most frequent diagnosis, in approximately 70% of the patients, was rheumatoid arthritis (RA). Radionuclide plus GC was injected into 20 radio-carpal joints, 8 elbow joints, 2 gleno-humeral joints and 7 finger joints. Placebo plus GC was injected into 20 radio-carpal joints, 5 elbow joints, 1 gleno-humeral joint and 5 finger joints. One patient in Group A died from non-RSO-related cardiac arrest.

Six months after treatment, the response rate was 69% (25/36) in group A and 29% (9/31) in group B (p=0.001). The mean ± SD CCI was 6.7 ± 3.2 in group A and 3.3 ± 3.8 in group B (p=0.001). Twelve months after treatment, the response rate was 69% (25/36) in group A and 32% (8/25) in group B (p=0.004). The mean ± SD CCI was 6.8 ± 3.3 for group A and 4.2 ± 4.7 for group B (p=0.046). The patients reported no treatment-related complaints, and no adverse physical effects were detected at the clinical examinations. No correlations were found between the mean CCI at 6 months and baseline characteristics of the joints.

In conclusion, RSO treatment of upper extremity joints with radionuclide plus GC shows a significantly higher response rate compared to that of placebo plus GC.

In **chapter 4** the results of a prospective trial on the effect of radionuclide leakage from the joint on the therapeutic effect of RSO of the upper extremity joints are described. The secondary aims were to determine whether baseline clinical variables or patient characteristics could predict leakage and to examine the differences in leakage between ^{169}Erbium and ^{186}Rhenium. The radiation doses to the non-target organs were estimated.

Thirty-seven RSOs were performed in 31 patients. One patient died from non-RSO-related cardiac arrest. The response rate was 69% (25/36) both at 6 and 12 months, with a mean CCI of 6.7±3.2, and 6.8±3.3, respectively. There was leakage to the lymph nodes and/or to the liver/spleen in 68% (25/37). The mean leakage to the lymph nodes was 1.7 ± 2.7% of the injected dose (range 0-9.9%). The median leakage to liver/spleen was 0.2% (range 0-6.8%). Leakage was detectable in 5 of the 11 non-responders (45%), and in 20 of the 25 responders (80%) (p=0.06). In the 11 non-responders, the mean leakage to the lymph nodes was 0.4% ± 0.7% versus 2.4% ± 0.8% in the 25 responders (p=0.03). The median leakage to the liver/spleen was 0% for non-responders and 0.3% for responders (p=0.4).

There was significantly less leakage of ^{169}Erbium than of ^{186}Rhenium, with the mean

leakage to the lymph nodes of 0.11 ± 0.3% versus 2.1 ± 2.8%, respectively (p=0.001) and a median leakage to the liver/spleen of 0% versus 0.5%, respectively (p=0.006). Leakage to non-target organs was seen in only 1 of 7 RSO treatments (14%) with ^{169}Erbium versus 20 of 30 (80%) with ^{186}Rhenium (p=0.002). The only significant correlation with leakage to the lymph nodes was the patient's age at the time of injection (r=-0.58, p=0.0001).

The maximal dose measured in a single lymph node was 86 Gy after RSO with ^{186}Rhenium, and the maximal dose to the liver/spleen was 0.012 Gy. Using ^{169}Erbium, the maximal dose to a lymph node was 3.0 Gy. Negative effects of these relative high single lymph node dose are not described in literature or experienced in clinical practice. However, there are no specific studies on this topic.

In conclusion, leakage of radionuclides from the joint to non-target organs did not negatively influence the effect of RSO. Only the patient's age at the time of the injection can predict leakage. Furthermore, ^{169}Erbium leaks significantly less from the joint than ^{186}Rhenium.

In **chapter 5** the effects of intra-articular ^{90}Yttrium distribution on the clinical effect of RSO of the knee and on ^{90}Yttrium leakage from the joint are described.

The clinical effects of intra-articular ^{90}Yttrium plus GC versus placebo plus GC were compared in a randomised Dutch multicentre clinical trial (9). Radionuclide distribution was scored as mainly diffuse or mainly focal.

Seventy-eight RSOs had been performed in 69 patients; in 9 patients, both knees were treated. Patients suffered mainly from undifferentiated arthritis (42%) or RA (28%). ^{90}Yttrium was "mainly diffuse" in 54% of the joints and "mainly focal" in 46%. The clinical results were not significantly different between the two groups: The response rate was 40% for the "mainly diffuse" distribution group and 56% for the "mainly focal" distribution group. The CCI scores did not correlate with the four classes of distribution, nor could they be predicted by distribution. No leakage to the lymph nodes was detected. The mean leakage of ^{90}Yttrium was 0.4±0.7% to the liver and 1.1±1.2% to the spleen. Leakage to the liver was significantly less for the "mainly diffuse" distribution group (0.2±0.4%) than for the "mainly focal" distribution group (0.9±0.8%; p<0.0001). Similar results for the two groups were found for leakage to the spleen: 0.6±0.4% versus 1.6±1.3%, respectively, p=0.04. The clinical effect, i.e. the CCI score, did not correlate with leakage.

In conclusion, intra-articular ^{90}Yttrium distribution did not influence the clinical effect of RSO of the knee. RSO of the knee is effective in approximately 50%. Similarly, leakage from the joint did not have an (adverse) effect on the clinical results.

In **chapter 6** we performed a broad systematic literature review on the effectiveness of RSO with ^{169}Erbium, ^{186}Rhenium or ^{90}Yttrium and in addition we did meta-analyses of the effects of these radionuclides using only comparative clinical trials.

Two investigators independently searched medical Medline, Embase, Cochrane Library

and CINAHL databases for relevant publications. Criteria for inclusion of the publication in the analysis included publication in English, a minimum 6-month follow-up time in the study, definition of the joint disease, and a report of the outcome of at least 5 RSO procedures. The included articles were scored for quality using the Oxford Centre of Evidence-based Medicine levels of evidence for therapy studies (which range from level 1, systemic review to level 5, expert opinion) (http://www.cebm.net/index.aspx?o=1025).

Seventy studies were included (4 level 1b studies, 15 2b studies, and 51 level 4 studies). The reported success rates of ^{169}Erbium-RSO and ^{186}Rhenium-RSO ranged from 69-100% at 6 months and from 54-100% at ≥12 months; for ^{90}Yttrium, the success rates were 24-100% and 29-94%, respectively. However, clearly there were differences in criteria and definitions of effect between studies and flaws in study design.

For the meta-analyses, data from studies comparing the effect of RSO with that of GC or saline injection were pooled. At 6 months, the pooled odds ratio favouring RSO of the knee with ^{90}Yttrium over control was 4 (CI 95% 1.2-14; p=0.02), and at 12 months the ratio was 1.7 (CI 95% 0.69-4; p=0.26). For RSO of small joints with ^{169}Erbium or ^{186}Rhenium compared to control, the pooled odds ratio at 6 months was 2 (CI 95% 0.66-6; p=0.22), and at 12 months, it was 2 (CI 95% 1.09-3.5; p=0.03). Differences in study design, e.g. comparison of isotope with or without GC versus GC or placebo, respectively, differences in the used GC and different inclusion criteria, e.g. failure or not to previous intra-articular GC injection could challenge the validity of the pooling.

In conclusion, the reported success rates of RSO are high. Differences in the effects of RSO versus GC injection are less evident; there is marked heterogeneity in study design of the (small number of) comparative studies.

General discussion

Effect of RSO

RSO and the therapeutic effects of RSO in treating synovitis are being studied for decades. Clinical parameters, imaging modalities, arthroscopy, and histology have been used to assess the effects of RSO (10-19). However, no single, validated, standardised method is routinely used to measure the effects of RSO. It has not been determined whether differences in RSO assessment methodology influence the findings.

Differences in randomised trial study design have complicated efforts to compare the results of RSO studies (9,18-35). Some studies differ in what is compared: isotopes with or without GC versus saline, GC, osmic acid, or surgical synovectomy, for example. Studies also differ in terms of which GC is used, in terms of the inclusion criteria (e.g. previous failure with intra-articular GC injection), and in terms of the underlying diseases causing synovitis.

Overall, RSO seems to achieve the best results for RA, followed by other inflammatory arthritides and hemophilic hemarthrosis. RSO is least effective for patients with osteoarthritis (36-39).

Few studies have been conducted to determine which patients benefit most from RSO, or how to best select candidates for RSO. A low radiological damage score, lack of joint instability and/or axial deviation, and a body mass index below the 85th percentile are characteristics in literature associated with favourable outcomes with RSO of the knee (40).

The reported success rates of RSO ranged from 54-100% for ^{169}Erbium and/or ^{186}Rhenium and 24-100% for ^{90}Yttrium, respectively. Meta-analyses of clinical trials showed a pooled odds ratio of 4 (CI 95% 1.2-14; p=0.02) at 6 months, favouring RSO of the knee with ^{90}Yttrium over control (saline or GC). In contrast, at 12 months the ratio was 1.7 (CI 95% 0.69-4; p=0.26). For RSO with ^{169}Erbium or ^{186}Rhenium compared to control, the pooled odds ratio at 6 months was 2 (CI 95% 0.66-6; p=0.22), and at 12 months it was 2 (CI 95% 1.09-3.5; p=0.03). ^{90}Yttrium and ^{169}Erbium are more effective than saline. The efficacy of ^{169}Erbium or ^{186}Rhenium was equal to GC. In two studies, ^{169}Erbium or ^{186}Rhenium plus GC was found to be superior to GC alone. ^{90}Yttrium was more effective than GC in 2 studies, and equally effective in 1 study. Two studies showed comparable success rates between ^{90}Yttrium plus GC and GC alone. However, some interpreted the results of Jahangier et al. as supporting RSO of the knee with ^{90}Yttrium (41,42). ^{90}Yttrium RSO was neither superior nor inferior to osmic acid or surgical synovectomy in treating synovitis.

The differences in RSO study design make it difficult to determine how RSO should be performed and to identify the best candidates for RSO. Our results suggest that RSO should consist of injection with both a radioisotope and GC in addition to immobilization. The best candidates for RSO are patients with persistent synovitis of one or a few joints in whom the disease in other joints is fairly well controlled after 1 intra-articular GC injection at the outpatient clinic or patients with recurrent synovitis of one or a few joints in whom the disease in other joints is fairly well controlled after 1 intra-articular GC injection within 3 months. The persistent synovitis should not remain untreated for too long prior to RSO, and there should be minimal radiological damage.

Leakage

Leakage of the isotope from the joint to non-target organs is a potential drawback of RSO. In our experience, leakage to non-target organs for these radiopharmaceuticals is minimal. However, leakage of up to 70% of the injected radionuclide has been described in a study of RSO with ^{90}Yttrium (43). Leakage of ^{169}Erbiuim is also generally low (13). The maximal leakage for ^{186}Rhenium colloids is 9.9% (12).

In theory, the following factors can increase leakage: joint mobilization; intra-articular hydrostatic pressure due to synovial fluid; injection technique; the grade of inflammation as a

measure of hypervascularity; the interference of X-ray contrast with the radiopharmaceuticals (especially ethylenediaminetetraacetic acid [EDTA], which can chelate radiocolloids and allow the dissolved radionuclide to leak more easily; and colloid particle size.

Immobilization is beneficial for the clinical effect of RSO and can decrease leakage (13). The influence of hydrostatic pressure within the joint on leakage has not been studied, but common sense dictates that the clinician should lower the intra-articular pressure by aspirating as much synovial fluid as possible before RSO. In addition, aspiration will remove the intra-articular inflammatory cytokines too. Performing the injection smoothly, so that the tissue damage is minimized, could also decrease leakage.

Theoretically, the grade of hypervascularity and/or hyperpermeability could influence leakage, especially if the radiocolloids are chelated. Adding GC to the radiocolloids in RSO can decrease hypervascularity as a consequence of inflammation and thus inhibit leakage. In addition to inhibiting leakage, the anti-inflammatory effects of GC can bridge the lag phase from injection time to the time at which the β-irradiation starts to have an effect.

Interference of GC, X-ray contrast, and anaesthetics with the stability of radiocolloids has been studied in vitro. EDTA-containing X-ray contrast mobilized 5-20% of ^{169}Erbium and ^{90}Yttrium out of the colloids; triamcinolone did not affect stability in the presence of synovial fluid (44). However, Franssen et al. found no significant differences in urinary excretion of ^{90}Yttrium after RSO using contrast agents with or without EDTA in vivo (45).

Next to joint immobilization after RSO, we believe that particle size of the colloids is the most important factor affecting leakage. The appropriate particle size is considered to be 2000 to 5000 nm (46). Colloidal ^{186}Rhenium-sulfide is 50-300 nm in size, ^{90}Yttrium colloid is 200 nm, and ^{169}Erbium is 2000-3000 nm (Schering-CIS Bio International, France); another source states that ^{90}Yttrium colloid is 100 nm (GE Amersham Healthcare).

Distribution

No association has been found between intra-articular distribution of ^{90}Yttrium and the clinical effects of RSO of the knee, in agreement with others (15). However, in RSO of the knee with ^{153}Samarium, there was a trend towards earlier relapse of synovitis after poor intra-articular distribution (47). Despite bending of the knee, distribution was “mainly diffuse” in only 54% of the joints. Since all patients had persistent synovitis, intra-articular septa or large synovial folds could have interfered with intra-articular distribution. Increasing the injected volume could accomplish a more homogeneous distribution. However, this and the influence on leakage have not been studied yet. Leakage of ^{90}Yttrium from the joint was decreased if ^{90}Yttrium was distributed diffusely in the joint cavity. One of the explanations for these observations could be higher pressure due to intra-articular septa or large synovial folds in focal distribution inducing more leakage.

General conclusions

RSO of the ankle and upper extremity joints is effective; RSO of the knee is less effective. RSO of the upper extremity joints can be recommended in persistent synovitis after failure to an outpatient intra-articular GC injection. Patient characteristics can not predict the outcome of RSO in upper extremity joints. Leakage and inhomogeneous distribution seem clinically not important and do not impair the effect of RSO.

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Chapter 8

Nederlandse samenvatting voor leken met discussie en conclusies

Inleiding

In dit proefschrift worden verschillende aspecten van radiatiesynovectomie, ofwel radiosynoviorthese (RSO) besproken. RSO is een behandeling van een reumatisch ontstoken gewricht door toediening van een radioactieve stof in dat gewricht.

Gewrichtsontsteking komt relatief veel voor. Gelukkig is gewrichtsontsteking in beginsel op meerdere manieren te behandelen. Daarbij is ook RSO een optie, maar zeker niet in de eerste fase of voor alle gewrichten. De behandelend arts schrijft meestal eerst ontstekingsremmende medicijnen zoals naproxen, diclofenac of ibuprofen voor en eventueel langwerkende antireumatica, zoals methotrexaat of de zogeheten biologische middelen, zoals anti-tumor necrosis factor. Niet zelden worden ook glucocorticoïden (GC) gebruikt, als tablet (prednison) of als gewrichtsinjectie.

Naast medicijnen zijn er niet-medicamenteuze behandelingen: fysiotherapie, ergotherapie met aanpassingen en voorzieningen, zoals spalken (die een ontstoken gewricht locale rust geven en relatieve overbelasting voorkomen) naast veranderingen in leefstijl. In een late fase kan een corrigerende gewrichtsoperatie noodzakelijk zijn.

Helpt medicamenteuze therapie niet voldoende en is er één of een beperkt aantal gewrichten ontstoken, dan komt vaak synovectomie als therapie in beeld. Er zijn drie methoden van synovectomie: chirurgische en chemische synovectomie en RSO. Bij chirurgische synovectomie wordt het ontstoken gewrichtskapsel verwijderd; bij chemische synovectomie en RSO wordt het ontstoken gewrichtskapsel afgebroken.

Hier volgt voor geïnteresseerden zonder professionele kennis van dit onderwerp een beknopte uiteenzetting van de zes hoofdstukken van dit proefschrift, met conclusies, algehele discussie en slotconclusie.

Hoofdstuk 1 beschrijft de vraagstellingen van het proefschrift en introduceert het begrip RSO. Hierbij wordt in een ontstoken gewricht een radioactieve stof toegediend. Ontstekingscellen in het gewrichtskapsel nemen deze stof op en verspreiden die door het hele gewricht. De straling levert tot op afstand van enkele millimeters energie aan het ontstoken gewrichtskapsel af. Hierdoor wordt de ontsteking geremd, wordt het ontstoken gewrichtkapsel dunner en stopt mogelijk zelfs - tijdelijk - de progressie van de gewrichtsschade.

De enige commercieel verkrijgbare, voor RSO geschikte radioactieve stoffen zijn tegenwoordig ^{90}Yttrium-, ^{169}Erbium- en ^{186}Rhenium-eiwitdeeltjes (colloïden). De Europese Vereniging van Nucleaire Geneeskunde (EANM) beveelt deze radioactieve stoffen voor RSO ook aan.

RSO is niet een nieuwe behandelingsmethode. De eerste klinische resultaten van RSO zijn zelfs al gepubliceerd in 1952. Maar de resultaten van tot op heden gepubliceerde onderzoeken geven niet altijd een eenduidig beeld en zeggen niet alles. Zo kan RSO plaatsvinden mét en

zónder toevoeging van GC aan de gewrichtsinjectie met de radioactieve stof. De tot dusver in de vakliteratuur gerapporteerde resultaten van RSO zijn overwegend gebaseerd op RSO zónder toevoeging van GC. Bovendien hebben de meeste onderzoeken weinig tot geen rekening gehouden met al dan niet eerdere, poliklinisch in het gewricht gegeven GC injecties. Het behandelingsresultaat van RSO hangt er mogelijk van af of RSO als eerste gewrichtsinjectie wordt gegeven of pas als een of meerdere gewrichtsinjecties met GC onvoldoende hebben geholpen. In dat laatste geval zouden, door negatieve selectie, de resultaten wel eens slechter kunnen zijn. Daarnaast zijn de resultaten van eerdere onderzoeken naar RSO voornamelijk gebaseerd op behandeling van 'slechts' knie- en vingergewrichten, terwijl ook ontsteking in andere gewrichten van de bovenste extremiteit, zoals polsen, ellebogen en schouders veel voorkomt en in enkels. Een ander punt is dat er geen overeenstemming is in methoden om de effectiviteit van RSO te meten (alle onderzoeken gebruiken andere definities van succesvolle behandeling) noch over de duur van follow-up.

De mate van lekkage van de radioactieve stof uit het gewricht en het effect van deze lekkage op het effect van RSO zijn tot nu toe evenmin goed onderzocht. Hetzelfde geldt voor de invloed op het uiteindelijke effect van al dan niet gelijkmatige verdeling van de radioactieve stof in het gewricht na de injectie. Deze actuele, klinisch relevante onderwerpen komen aan de orde in dit proefschrift.

De vraagstellingen:

- Kan RSO van de knie, enkel en gewrichten van de bovenste extremiteit als effectief worden bestempeld?
- Valt RSO onder de internationale standaard 'evidence based medicine' (wetenschappelijk bewezen effectieve geneeskunde)?
- Zijn er kenmerken van patiënten, welke een effect van RSO kunnen voorspellen?
- Is bij RSO lekkage van de radioactieve stof uit het gewricht van klinisch belang?
- Is bij RSO de verdeling van de radioactieve stof in het gewricht van klinisch belang voor het effect?

Hoofdstuk 2 blikt terug op ons onderzoek naar het effect, de duur van het effect en de veiligheid van RSO bij patiënten met een aanhoudende gewrichtsontsteking van de enkel. Het onderzoek leverde tevens een schatting op van de mate van lekkage van de radioactieve stof uit dit gewricht. Daarbij is een indicatie van de stralingsdosis die het gewrichtskapsel krijgt toegediend relevant, evenals de dosis straling (uitgedrukt in Gray) die via lekkage terechtkomt in organen zoals lymfeklieren en lever.

In 22% van de gevallen bleef RSO zonder effect, maar in hetzelfde percentage bleek RSO een matig effect te hebben, dat gemiddeld 34 maanden aanhield. In de overige 56% van de gevallen trad een goed effect op, dat gemiddeld 41 maanden aanhield. De mate van lekkage,

uitgedrukt als percentage van de geïnjecteerde dosis, verschilde niet of nauwelijks tussen de groepen met verschillend behandelingsresultaat.

De stralingsdosis voor het gewrichtskapsel is, afhankelijk van de hoeveelheid lekkage, 2,76 tot 3,05 Gray (Gy). De gemiddelde lekkage ± standaarddeviatie voor alle procedures is 2,4 ± 3,0% voor lekkage naar de lymfeklieren en 0,8 ± 1,7% voor lekkage naar de lever. De maximale dosis straling die terechtkomt bij een enkele lymfeklier is geschat op 35 Gy bij een lekkage van 4%. Deze hoge dosis ontstaat doordat het gelekte isotoop de straling aan een zeer klein volume van één tot enkele mm^3 van de lymfeklier afgeeft. In de klinische praktijk en de wetenschappelijke literatuur zijn er geen aanwijzingen dat dit schadelijk is. De maximale dosis straling bij de lever op 0,0075 Gy.

Conclusies

Het succespercentage van RSO van de enkel was 78%, hoewel uiteindelijk bij alle patiënten de gewrichtsontsteking terugkeerde. Lekkage uit het gewricht heeft geen invloed op het effect van de RSO en is algemeen gering; RSO van de enkel lijkt derhalve veilig.

In **hoofdstuk 3** beschrijven we een dubbelblind onderzoek. Hierin vergelijken we het klinische effect van het in het gewricht toedienen van een *radioactieve stof* met GC (RSO en GC: groep A) met het klinische effect van een *nepmiddel* met GC (placebo en GC; groep B). De toediening vond plaats in aanhoudende ontstekingen van gewrichten van de bovenste extremiteit (vingers, polsen, ellebogen en schouders), nadat één poliklinische injectie met GC in het gewricht geen succes had opgeleverd.

De deelnemende patiënten werden willekeurig toegewezen aan groep A of groep B. Om zo nauwkeurig mogelijk resultaten te verkrijgen, zijn zes soorten beoordelingen meegewogen. Ten eerste: de beoordeling door de hoofdonderzoeker van de mate van beperking door de klachten: hoe 'erg' leek het gesteld te zijn met het ontstoken gewricht? Ten tweede was er de beoordeling door de patiënt zelf van de mate van pijn. Als derde scoorde de hoofdonderzoeker de gevoeligheid van het aangedane gewricht bij licht erop drukken (was er géén gevoeligheid of pijn, kromp de patiënt ineen of lag de mate van gevoeligheid hier ergens tussenin)? De vierde meeteenheid betrof de mate van zwelling van het gewricht, beoordeeld door de hoofdonderzoeker en de vijfde de beoordeling door de patiënt van het globale effect van de behandeling. Voelt hij of zij dat verbetering was opgetreden? Zo ja, in welke mate? Tot slot speelde de beoordeling door de hoofdonderzoeker van het globale effect van de behandeling een rol. Hoe schatte hij de mate van verbetering in?

Voor dit onderzoek zijn 68 injecties in het gewricht bij 44 patiënten (23 vrouwen, 21 mannen) geanalyseerd. Van alle gewrichten werden er 37 behandeld volgens het protocol van groep A en 31 volgens dat van groep B. Bij de meeste van de patiënten was sprake van reumatoïde artritis. In groep A zijn de resultaten van het toedienen van de radioactieve

stof en GC in 20 polsgewrichten, 8 ellebooggewrichten, 2 schoudergewrichten en 7 vingergewrichten vergeleken met die van het toedienen in groep B van het nepmiddel en GC in 20 polsgewrichten, 5 ellebooggewrichten, 1 schoudergewricht en 5 vingergewrichten.

Zes maanden na de injecties trad in groep A in 69% van de behandelingen effect op en in groep B in 29%. Deze percentages golden eveneens twaalf maanden na de injecties. Globaal gezegd geven deze getallen daarmee aan dat het toedienen van een radioactieve stof en GC een beduidend hoger effect geeft dan het toedienen van een nepmiddel en GC. Daarbij rapporteerden de patiënten geen therapiegerelateerde klachten en zijn evenmin lichamelijke bijwerkingen geconstateerd. Er werd geen verband gevonden tussen kenmerken van patiënten (zoals leeftijd) en het effect van RSO, zodat het voorspellen van het effect van RSO voor de behandeling niet mogelijk is.

Conclusie

In gewrichten van bovenste extremiteit geeft een injectie met radioactieve stof en GC (RSO) een beduidend hoger effectpercentage dan injectie met nepmiddel en GC (GC-injectie), indien een voorafgaande polikinisch gegeven GC-injectie onvoldoende effectief is gebleken.

Onderwerp in **hoofdstuk 4** is de invloed van lekkage uit het gewricht op het effect van RSO van gewrichten van de bovenste extremiteit. De secundaire vragen van de studie zijn: is de mate van lekkage voorspelbaar aan de hand van kenmerken van de patiënten (klinische variabelen, bijvoorbeeld leeftijd) en zijn er verschillen in lekkage tussen RSO met gebruik van ^{169}Erbium of ^{186}Rhenium? Verder geeft dit onderzoek een schatting van de stralingsdosis die door lekkage terechtkomt in organen.

Voor dit onderzoek zijn 37 RSO's bij 31 patiënten verricht. Zowel na zes als na twaalf maanden is goed effect gemeten bij 69% na de RSO's. Bij 25 van de 37 van de RSO's (68%) is lekkage naar lymfeklieren en lever/milt vastgesteld; bij 17 RSO's betreft dit zowel lekkage naar de lymfeklieren als naar lever/milt. Bij 6 RSO's was er alleen lekkage naar de lymfeklieren, in 2 gevallen alleen lekkage naar lever/milt. De lekkage was in het algemeen gering. De gemiddelde lekkage naar lymfeklieren was 1.7 (min 0 - max 9.9%). Het gemiddelde voor lekkage naar lever/milt was 0.2% (min 0 - max 6.8%).

Bij 45% van de RSO's die geen effect hadden, trad lekkage op. Bij de RSO's die wél effect hadden, is het lekpercentage hoger, namelijk 80%. De gemiddelde lekkage naar lymfeklieren is bij effectieve RSO's ook hoger dan bij niet-effectieve RSO's. Ditzelfde geldt, in mindere mate, voor de gemiddelde lekkage naar lever/milt: 0.3% versus 0% van de in het gewricht toegediende stralingsdosis. Verder blijkt dat RSO met ^{169}Erbium beduidend lagere lekkages geeft dan RSO met ^{186}Rhenium. Dit geldt voor zowel de gemiddelde lekkage naar lymfeklieren als die naar lever/milt. Bij slechts 1 van 7 RSO's met ^{169}Erbium is lekkage naar organen opgetreden, bij ^{186}Rhenium was dit het geval bij 20 van 30 RSO's (80%).

Wat betreft het verband tussen klinische uitgangsvariabelen (kenmerken van de patiënt) en lekkage: er is alleen een verband gevonden tussen lekkage naar lymfeklieren en de leeftijd op het moment van injectie: bij oudere patiënten was er minder lekkage. De andere patiëntenkarakteristieken kunnen lekkage niet voorspellen.

Tot slot komt uit dit onderzoek naar voren dat de maximale radioactieve dosis voor een lymfeklier beduidend hoger is bij RSO met ^{186}Rhenium dan bij RSO met ^{169}Erbium door de hogere lekkage. Er zijn geen aanwijzingen dat de straling door lekkage schadelijk is. Bij RSO met ^{169}Erbium is geen lekkage naar lever/milt geconstateerd.

Conclusies

Lekkage is in het algemeen gering. Lekkage vermindert níet het klinische effect van RSO. Alleen de leeftijd op het moment van injectie kan lekkage voorspellen, bij oudere patiënten minder lekkage. Lekkage is beduidend lager bij RSO met ^{169}Erbium dan bij RSO met ^{186}Rhenium.

In **hoofdstuk 5** werd in een dubbelblind onderzoek naar het effect van RSO van de knie gekeken of al dan niet gelijkmatige verdeling van het radioactieve middel (^{90}Yttrium) na toediening in het gewricht en lekkage van het radioactieve middel uit het gewricht van invloed waren op het effect van RSO.

Voor dit onderzoek zijn bij 69 patiënten 78 RSO's uitgevoerd; bij 9 patiënten zijn beide knieën behandeld. Ongedifferentieerde gewrichtsontsteking (42%) of reumatoïde artritis (28%) waren onder deze patiënten de meest voorkomende ziekten.

Toedienen van ^{90}Yttrium in het kniegewricht bleek een voornamelijk gelijkmatige verdeling op te leveren bij 54% van de RSO's, tegenover een voornamelijk ongelijkmatige of locale verdeling bij de overige 46% RSO's. Er was geen significant verschil in klinisch effect tussen beide groepen; de mate van homogeniteit bleek het klinisch effect niet te kunnen voorspellen.

Verder werd geen lekkage naar lymfeklieren aangetoond. Wel was er geringe lekkage naar de lever, evenals iets meer lekkage naar de milt. Lekkage naar de lever is bij een voornamelijk gelijkmatige verdeling van het ^{90}Yttrium beduidend lager dan bij voornamelijk ongelijkmatige verdeling. Ook de gemiddelde lekkage naar de milt is lager bij een voornamelijk gelijkmatige verdeling van deze radioactieve stof.

Conclusies

Een inhomogene verdeling van het radioactieve ^{90}Yttrium in het kniegewricht relatief kort na injectie vermindert het klinisch effect niet. Lekkage uit het gewricht beïnvloedt het klinisch effect evenmin. Ongelijkmatige of locale verdeling van de radioactieve stof na injectie is wel geassocieerd met lekkage uit het gewricht.

Hoofdstuk 6 geeft een systematisch overzicht van de resultaten van eerdere onderzoeken naar de effectiviteit van RSO met ^{169}Erbium, ^{186}Rhenium of ^{90}Yttrium. Twee auteurs hebben, onafhankelijk van elkaar, medische databases op relevante publicaties onderzocht. Zij hanteerden daarbij de volgende criteria:
• publicatie in het Engels
• minimale follow-up van 6 maanden
• vermelding van aard van de gewrichtsziekte
• vermelding van resultaten van minimaal 5 RSO's per onderzoek.

Voor dit systematische overzicht zijn uiteindelijk zeventig studies gebruikt. De hierin beschreven succespercentages voor RSO's met ^{169}Erbium/^{186}Rhenium variëren van 69-100% na 6 maanden en van 54-100% na 12 maanden of langer. Voor ^{90}Yttrium-RSO zijn de succespercentages 24-100% na 6 maanden en 29-94% na 12 maanden of langer. Er werden in de onderzoeken wel heel verschillende criteria en definities voor succes van de behandeling gehanteerd.

Voor een schatting van het gemiddelde effect van verschillende onderzoeken (poolen van het effect met meta-analyse) zijn de studies gebruikt die het effect van RSO met ^{90}Yttrium hebben vergeleken met dat van een injectie in het gewricht met nepmiddel of GC (vergelijkende studie). De kans dat na 6 maanden het effect van RSO van de knie met ^{90}Yttrium effectiever was dan injectie met placebo of GC is 4 op 1. Na 12 maanden was de kansratio 1,7 op 1. Deze resultaten betroffen 5 onderzoeken met effect na 6 maanden en 3 onderzoeken met effect na 12 maanden. Het effect beschreven in 5 onderzoeken (effect na 6 maanden) en 6 onderzoeken (effect na 12 maanden) van RSO van de kleinere gewrichten met ^{169}Erbium/^{186}Rhenium werd ook gepoold. Hierbij was de kans op een beter effect van RSO vergeleken met toediening van nepmiddel of GC na 6 maanden zowel als na 12 maanden 2 op 1.

De insteek en opzet van de onderzoeken variëren echter nogal. Zo is RSO in de ene studie mét, en in de andere studie zónder toevoeging van GC onderzocht, zijn er verschillen in de soort GC en is het effect van RSO soms wel, soms niet onderzocht na onvoldoende effectiviteit van een poliklinisch toegediende GC-injectie. Deze verschillen zijn logischerwijs van invloed op de betrouwbaarheid van het systematische overzicht en de meta-analyse.

Conclusies

De effectpercentages van RSO zijn hoog, maar de verschillen in effect vergeleken met toepassing van een GC-injectie in het gewricht zijn minder duidelijk. Belangrijke kanttekeningen zijn dat er duidelijke verschillen in studieopzet zijn en dat het aantal vergelijkende studies klein is.

Discussie

RSO en het therapeutische effect ervan zijn al tientallen jaren onderwerp van onderzoek. Maar er is nog geen gevalideerde, gestandaardiseerde methode voor het meten van het effect van RSO, evenmin is onderzocht of de verschillen in methoden het gemeten effect beïnvloeden. Zo bemoeilijken verschillen in studieopzet van de dubbelblinde onderzoeken een heldere vergelijking en interpretatie van de resultaten.

'Beste' patiënten

Uit literatuur blijkt dat RSO in het algemeen de beste resultaten geeft bij reumatoïde artritis, gevolgd door andere reumatische gewrichtsontstekingen en gewrichtsontsteking door gewrichtsbloeding door een bloedstollingziekte (hemofilie). RSO is het minst effectief bij ontsteking door slijtage (artrose). Welke patiënten het meeste baat hebben bij RSO en hoe deze patiënten het best te selecteren, is verder nauwelijks onderzocht. In de literatuur beschreven patiëntkarakteristieken voor een gunstige uitkomst bij RSO van de knie zijn geen of weinig beschadiging van het te behandelden kniegewricht op de röntgenfoto en afwezigheid van gewrichtsinstabiliteit (en/of standsafwijking) van de te behandelen knie en van duidelijk overgewicht van de patiënt.

Vanwege de diversiteit van de literatuur is het moeilijk vast te stellen hoe we RSO het best kunnen uitvoeren en wie de beste kandidaten ervoor zijn. Onze resultaten suggereren dat, naast het toedienen van een van de radioactieve stoffen, óók GC zou moeten worden toegediend. De beste patiënten voor RSO, naar onze mening, zijn patiënten die kampen met aanhoudende gewrichtsontsteking of snel terugkerende gewrichtsontsteking na een poliklinische GC-injectie in één of slechts enkele gewrichten, bij wie de ziekte verder goed onder controle is (anders is intensievere, systemische medicamenteuze therapie aangewezen). De duur van de aanhoudende gewrichtsontsteking zou niet te lang mogen zijn zodat de ontstane gewrichtsschade minimaal is.

Succespercentages van RSO

De succespercentages van ^{169}Erbium/^{186}Rhenium-RSO variëren van 54-100% en van ^{90}Yttrium-RSO van 24-100%. Bundeling van klinische onderzoeken geven de volgende kansratio's: kansratio van 4 (95% betrouwbaarheidsinterval; 1,2-14) dat na 6 maanden RSO van de knie met ^{90}Yttrium beter is dan placebo of GC en 1.7 (95% betrouwbaarheidsinterval; 0.69-4) na 12 maanden. Voor RSO van de kleinere gewrichten met ^{169}Erbium/^{186}Rhenium zijn de kansratio's respectievelijk 2 (95% betrouwbaarheidsinterval; 0.66-6) na 6 maanden en 2 (95% betrouwbaarheidsinterval; 1.09-3.5) na 12 maanden. ^{90}Yttrium en ^{169}Erbium zijn effectiever dan placebo. ^{169}Erbium of ^{186}Rhenium plus GC is effectiever dan GC. ^{90}Yttrium is

effectiever dan GC in 2 studies en vergelijkbaar effectief in 1 studie. In 2 studies is het effect van ^{90}Yttrium plus GC gelijk aan dat van GC. ^{90}Yttrium is niet superieur noch inferieur aan osmiumzuur of chirurgische synovectomie.

Oorzaken van lekkage

Lekkage van de radioactieve stof uit het gewricht is één van de nadelen van RSO. In onze ervaring is lekkage gering, al geeft de onderzochte literatuur blijk van andere getallen; zo wordt een lekkage van 70% beschreven bij RSO met ^{90}Yttrium en is de maximale lekkage voor ^{186}Rhenium colloïden 9,9% van de toegediende dosis. Lekkage van ^{169}Erbiuim is gering. In theorie kunnen de volgende factoren lekkage vergroten:

1. te veel bewegen van het net behandelde gewricht (te voorkomen door spalken)
2. hoge druk binnen het behandelde gewricht door veel gewrichtsvocht door ontsteking
3. de injectietechniek (de mate van juiste plaatsing van de injectie; al dan niet volledig verwijderen van gewrichtsvloeistof; de mate van verdeling binnen het gewricht)
4. de ernst van de ontsteking overeenkomend met de doorbloeding binnen het gewricht (veel doorbloeding, meer kans op lekkage)
5. interactie van röntgencontrast met de radioactieve stoffen, met name ethyleen-diamine-tetra-acetaatzuur (EDTA). EDTA kan van de radioactieve verbindingen het radioactieve molecuul losmaken dat, doordat het kleiner is, gemakkelijker kan lekken dan de radioactieve verbinding)
6. de deeltjesgrootte van de radioactieve verbindingen.

Voorkómen van lekkage

Immobilisatie (spalken) is gunstig voor het klinisch effect en kan lekkage verminderen. De invloed van druk door het gewrichtsvocht in het gewricht is tot op heden niet onderzocht. Het is logisch de druk te verlagen door zoveel mogelijk gewrichtsvocht te verwijderen voordat de radioactieve stof en GC worden toegediend. Ook een adequate, weinig traumatiserende punctie helpt lekkage zo gering mogelijk te houden.

In theorie kan ook de graad van doorbloeding en/of doorgankelijkheid van het gewrichtskapsel lekkage (negatief) beïnvloeden. GC toevoegen aan de radioactieve verbindingen maakt het mogelijk de verhoogde doorbloeding, als gevolg van de ontsteking, op korte termijn te doen verminderen of verdwijnen. Mogelijk vermindert dit de lekkage. Een ander voordeel van GC is het overbruggen van de tijd tussen injectie en het begin van het effect van RSO: GC helpt namelijk binnen één tot enkele dagen en het effect van RSO laat langer op zich wachten. Daarnaast kan GC (chemische en bestralings) irritatie van het gewricht met pijn door de toegedoende stoffen kort na RSO voorkómen.

De invloed van GC, röntgencontrast en verdovingsmiddelen op de stabiliteit van radioactieve verbindingen is buiten het lichaam (in vitro) onderzocht. EDTA bevattend

röntgencontrast kan 5-20% van het ^{169}Erbium en ^{90}Yttrium uit de colloïdverbinding losmaken. In gewrichtsvocht heeft GC geen effect op de stabiliteit van de radioactieve verbindingen. De grootte van de colloïd-deeltjes bepaalt naar onze mening, naast immobilisatie, in belangrijkste mate lekkage.

Gelijkmatige verdeling in het gewricht

Er is geen verband gevonden tussen de verdeling van ^{90}Yttrium in het gewricht en het klinisch effect van RSO van de knie, overeenkomend met resultaten in de literatuur. In ons onderzoek was ondanks het éénmalig buigen van de knie de verdeling slechts in 54% voornamelijk homogeen. Aangezien alle patiënten een aanhoudende gewrichtsontsteking hebben, kunnen schotten in het gewricht en grote gewrichtskapselvlokken een homogene, diffuse verdeling belemmerd hebben. Lekkage van ^{90}Yttrium uit het gewricht was minder indien de distributie meer diffuus was. Mogelijk dat de druk bij een ongelijkmatige verdeling en zeker bij locale opeenhoping hoger is, waardoor meer lekkage optreedt.

Conclusies

RSO van de enkel en bovenste extremiteitgewrichten is een effectieve behandeling; RSO van de knie is minder effectief. RSO van de bovenste extremiteitgewrichten kan aanbevolen worden als ‘evidence based medicine’ na falen op een poliklinische GC-injectie. Kenmerken van patiënten kunnen het effect van RSO van gewrichten van bovenste extremiteiten niet voorspellen. Lekkage en ongelijke verdeling zijn klinisch niet van belang en verminderen het effect van RSO niet.

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Curriculum vitae

Friso M. van der Zant wordt op 6 december 1964 geboren te Amersfoort. In 1983 behaalt hij het Gymnasium β diploma aan het Stedelijk Gymnasium Johan vanOldenbarnevelt te Amersfoort. De studie geneeskunde volgt hij aan de Vrije Universiteit te Amsterdam; deze wordt met het behalen van het arts-examen in 1990 afgesloten. Hij vervult de militaire dienstplicht en werkt ongeveer één jaar voor de firma Mallinckrodt Medical. Van 1993-1997 is hij in opleiding tot nucleair geneeskundige in het AMC, opleider prof. dr. E.A. van Royen. Vanaf 1997 is hij werkzaam op de afdeling nucleaire geneeskunde in het MCA en sedertdien zijn in de loop der tijd de ideeën voor wetenschappelijk onderzoek naar radiosynoviorthese ontstaan. Dit heeft uiteindelijk geleid tot het proefschrift, dat voor u ligt.

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